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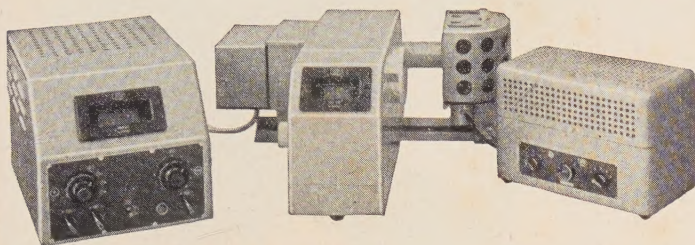
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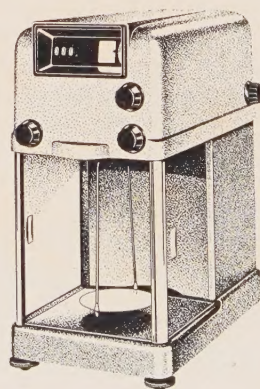


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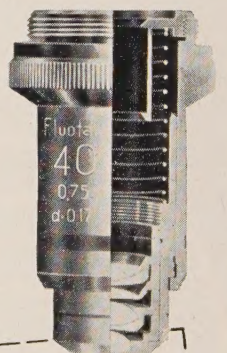
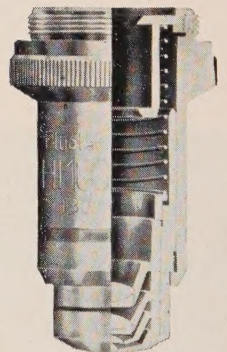


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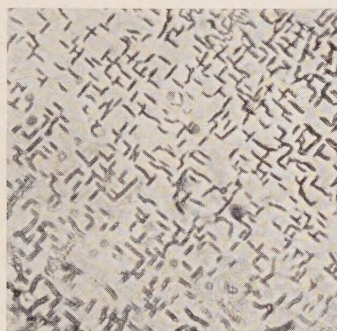
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Über die orientierte Aufwachsung von Polyäthylen auf Steinsalz

Über orientierte Aufwachsungen von hochpolymeren organischen Stoffen ist bisher nichts bekannt geworden.

Nachdem es in neuerer Zeit gelungen ist, einerseits Einzelkristalle von linearem Polyäthylen herzustellen¹ und andererseits Kristalle der in ihrer Kristallstruktur dem Polyäthylen sehr ähnlichen² niedermolekularen Paraffine zur orientierten Aufwachsung auf Alkalihalogenuiden zu bringen³, bot sich das System lineares Polyäthylen - NaCl zur Prüfung der Frage, ob hochpolymere organische Stoffe orientiert aufzuwachsen vermögen, an.



Orientierte Aufwachsung von Polyäthylen auf (001) NaCl

Versuche mit einem linearen Polyäthylen (Marlex. $M = 105\,000$) führten ohne weiteres zu den gesuchten Aufwachsungen. Das lineare Polyäthylen wurde aus einer 0,06prozentigen Lösung in Dekalin auf die Spaltfläche (001) eines auf 90° erhitzten Steinsalzkristalls aufgebracht. Das Polyäthylen orientierte sich auf (001) von NaCl in Nadeln mit der Nadellängsachse $\parallel [110]$ und $[1\bar{1}0]$.

J. WILLEMS und I. WILLEMS

Krefeld, Tiergartenstrasse 21, den 12. August 1957.

Summary

Orientated overgrowth of linear polyethylene on rock-salt is described. The needle-shaped crystals of polyethylene are orientated on (100) of NaCl with the long axe of the needles parallel to $[110]$ and $[1\bar{1}0]$.

¹ R. JACCODINE, *Nature* 176, 305 (1955). - P. H. TILL, Jr., *J. Polymer Sci.* 24, 301 (1957).

² C. W. BUNN, *Trans. Faraday Soc.* 35, 482 (1939).

³ J. WILLEMS, *Naturwissenschaften* 42, 176 (1955).

On Chondroitin Sulphate and Mucoprotein from Cartilage

It has been proposed¹ that in mammalian hyaline cartilage chondroitin sulphate is present in two forms: about one third would be bound to a protein different from collagen to form a mucoprotein, the remainder being linked to collagen.

The present work was carried out on a product extracted from horse nasal septa cartilage. Aqueous solutions of 30% potassium chloride plus 1% potassium carbonate² were used in this extraction. After centrifuging, the extraction solutions were dialyzed and added with potassium acetate and alcohol at 0°C. The precipitates so obtained were redissolved and reprecipitated in a similar way and finally they were dried with absolute alcohol and ether.

The aim was to give a physicochemical picture of this product which will be referred to as MC.

The N content of MC (referred to the dry weight at 110°C) was 3.9%. Its amino acid composition, as revealed by paper chromatography, was as follows: aspartic acid, serine, glycine, glutamic acid, threonine, alanine, leucine (+++); ornithine, lysine, valine, phenylalanine (++); histidine, tyrosine, tryptophan, proline (+).

By paper electrophoresis (pH 2.0-10.0), it was found that MC was formed by two components. One was immobile and stained with light green and metachromatically with toluidine blue; the other one migrated towards the anode and only stained metachromatically with toluidine blue.

In the analytical ultracentrifuge, MC in phosphate buffer M/15, pH 7.0 exhibited a very diffuse and asymmetric boundary and it was impossible to obtain its sedimentation coefficient.

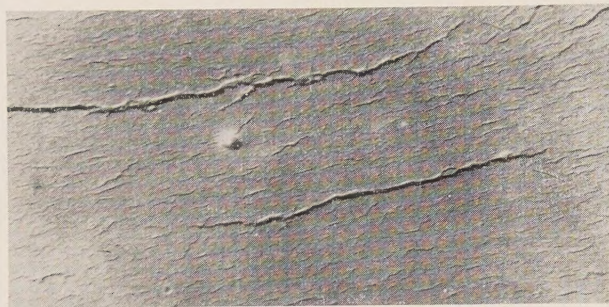
A light scattering study of MC in phosphate buffer as above made it possible to obtain the following values for the average molecular weight, dissymmetry, Z-average radius of gyration, respectively: $M_w = 1.75 \cdot 10^6$; $z = 2.05$; $R_z = 1100$ Å.

All the above results are easily explained if it is assumed that MC contains a certain amount of free polysaccharide besides the mucoprotein of high molecular weight. Owing to the relatively low molecular weight of chondroitin sulphate, the light scattering results must be referred to the mucoprotein. In this case too, using the

¹ J. SHATTON and M. SCHUBERT, *J. biol. Chem.* 211, 565 (1954).

² J. EINBINDER and M. SCHUBERT, *J. biol. Chem.* 185, 725 (1950).

same treatment of the Zimm plot as for a different mucoprotein preparation previously studied³ (according to the papers of SADRON and BENOIT⁴, and BENOIT⁵), it is possible to conclude that a polydisperse system of coils is the best model for the molecular shape of MC in salt solution.



Electron micrograph of MC ($1 \cdot 10^{-5}$ g/ml in distilled water). Magnification: $30000 \times$. Shadowing with gold-manganin at 20° .

An investigation with the electron microscope of extremely dilute aqueous solutions of MC showed the presence of fibrous structures (Figure). These fibres are thought to be formed by side aggregation of smaller units, possibly of mucoprotein and chondroitin sulphate molecules. They seem to confirm: (a) the previously postulated end-to-end arrangement of polysaccharide and polypeptides in the mucoprotein molecules⁶, and (b) the suggested possibility of linkages between acid groupings of chondroitin sulphate or mucoprotein molecules and basic groupings of other mucoprotein molecules when the ionic strength of the medium is very low and consequently the ionization is high⁷.

A more detailed account of this work will be published in due course elsewhere.

G. BERNARDI*, C. CESSI, and L. GOTTE

Centre de Recherches sur les Macromolécules, Strasbourg (France), Istituto di Patologia Generale, Università di Bologna (Italia), and Istituto di Istologia, Università di Padova (Italia), July 3, 1957.

Riassunto

Sono riferiti i risultati di uno studio chimico-fisico sul condroitinsolfato e sulla mucoproteina della cartilagine. È brevemente discusso il significato di questi risultati in relazione ad una struttura precedentemente proposta per la mucoproteina.

³ G. BERNARDI, *Nature* **180**, 93 (1957).

⁴ C. SADRON, H. BENOIT, M. DAUNE, *Int. Symp. macromol. Chem. (Milan-Turin, 1954)*.

⁵ H. BENOIT, *J. Polym. Sci.* **11**, 507 (1953).

⁶ G. BERNARDI, *Biochim. biophys. Acta* (in press).

⁷ G. BERNARDI, *C. r. Acad. Sci.* **244**, 1918 (1957).

* Present address: National Research Council, Division of Applied Biology, Ottawa, Canada.

The Structures of Ambrosin and Damsin¹

Two crystalline compounds, named ambrosin and damsins, have recently been isolated from *Ambrosia maritima* L., fam. Compositae, by ABU-SHADY and SOINE². The same authors carried out a thorough study of the oxidation and reduction of the two natural products and the following conclusions were made at that time. Ambrosin and damsins contain the same carbon skeleton and are tricyclic. The formation of an unidentified azulene on dehydrogenation of 'reduced ambrosin' suggested the presence of a substituted bicyclo-(5,3,0)-decane skeleton in these two natural substances. Finally the authors suspected a structural relation between ambrosin and helenalin.

Recent work on helenalin has shown that this sesquiterpene lactone is represented by I³. We have now used the information gained from the study of both helenalin (I) and tenulin⁴ (III) to deduce possible structures for ambrosin and damsins.

The azulene obtained previously² was characterized by a trinitrobenzene-adduct, m.p. $125-130^\circ$, and in our opinion represents the derivative of chamazulene (IV), m.p. 132° ⁵. This finding suggests that ambrosin and damsins belong to the guaianolides, a group of sesquiterpenes which are known to occur frequently in plants of the Compositae family.

The ultraviolet absorption spectrum of ambrosin ($\lambda_{\max}$ 217 m μ , ϵ 13465) cannot be reconciled with the presence of a cyclopentenone chromophore alone, because such systems are characterized by low extinctions. (Dihydrohelenalin V has $\lambda_{\max}$ 227 m μ , ϵ 7250 and tenulin III has $\lambda_{\max}$ 226 m μ , ϵ 7000.) The light absorption must therefore be due to two isolated chromophores and like in helenalin (I) ($\lambda_{\max}$ 220 m μ , ϵ 12200), the terminal methylene group in ambrosin must be conjugated with the γ -lactone ring. The second chromophore should therefore absorb like dihydrohelenalin (V) and we can conclude that ambrosin is in fact an α - or β -substituted cyclopentenone. The ready formation of bromoambrosin and particularly its light absorption ($\lambda_{\max}$ 248 m μ , ϵ 7025) strongly suggests that it is a α -bromo- β -alkyl cyclopentenone⁶ and ambrosin, therefore, is a β -alkylcyclopentenone. The evidence discussed thus far can be summarized in the partial symbols IX and X.

There is no conclusive evidence at hand which would allow a distinction between the two alternatives IX and X. However, tenulin (III), helenalin (I) and geigerin⁷, all isolated from Compositae, have been shown to be C_2 -ketones rather than C_3 -ketones and we would like to suggest, on biogenetic grounds, that ambrosin and damsins contain part structure IX.

¹ Terpenes VIII. Part. VII, G. BÜCHI and W. S. SAARI, *J. Amer. chem. Soc.* (in press).

² H. ABU-SHADY and T. O. SOINE, *J. Amer. pharm. Ass.* **42**, 387 (1953); **43**, 365 (1954).

³ G. BÜCHI and D. ROSENTHAL, *J. Amer. chem. Soc.* **78**, 3860 (1956). – V. HEROUT, M. ROMANUK, and F. SORM, *Coll. Czechosl. chem. Comm.* **21**, 1359 (1956). – R. ADAMS and W. HERZ, *J. Amer. chem. Soc.* **71**, 2456, 2551, 2554 (1949).

⁴ D. H. R. BARTON and P. DE MAYO, *J. chem. Soc.*, 1956, 142.

⁵ A. MEISELS and A. WEIZMANN, *J. Amer. chem. Soc.* **75**, 3865 (1953). – F. SORM, J. NOVAK, and V. HEROUT, *Coll. Czechosl. chem. Comm.* **18**, 527 (1953).

⁶ A. L. NUSSBAUM, O. MANCERA, R. DANIELS, G. ROSENKRANZ, and C. DJERASSI, *J. Amer. chem. Soc.* **73**, 3263 (1951). Bromohelenalin has $\lambda_{\max}$ 248 m μ , ϵ 6300; R. ADAMS and W. HERZ, *J. Amer. chem. Soc.* **71**, 2456, 2551, 2554 (1949).

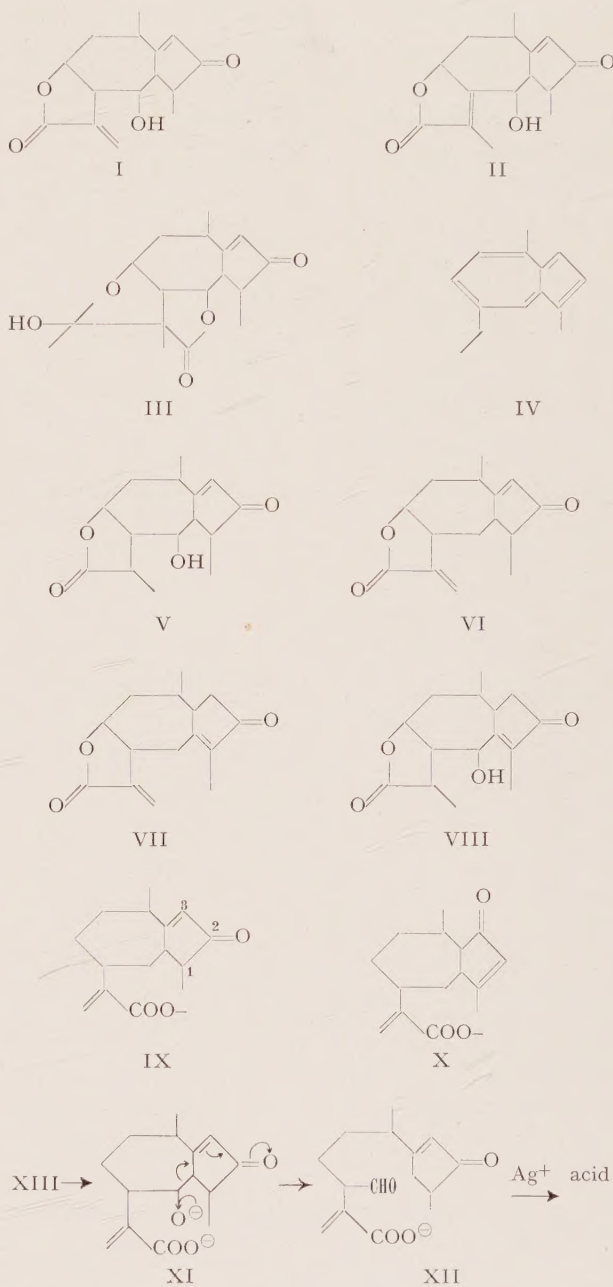
⁷ G. W. PEROLD, *J. chem. Soc.* **1957**, 47.

To develop the structures further we now have to differentiate between the two isomers VI and XIII. A distinction was possible as follows. According to ABU-SHADY and SOINE² ambrosin, like dihydrohelenalin (V), gives a positive Tollens test. The functionality undergoing oxidation cannot be derived from the α,β -unsaturated ketone *per se* (no β hydrogen) nor can it be a vinylogous α -hydroxyketone because helenolid (VI)⁸, neohelenolid (VII)⁹ and dihydroneohelenalin (VIII)⁹ all give *negative* Tollens tests. The simplest explanation of these findings is that ambrosin, on treatment with base undergoes, at least partly, a retroaldol cleavage (XI $\rightarrow$ XII), which is followed by oxidation of the aldehyde (XII) with silver ion. Ambrosin should therefore be XIII.

We now discuss the behavior of ambrosin and damsine on reduction. It has been shown previously¹⁰ that natural helenalin contains both I and isohelenalin (II) and that the isomers are not separable by crystallization. Helenalin (I) on catalytic hydrogenation yields dihydrohelenalin (V) which, however, is reduced rapidly to tetrahydrohelenalin. Isohelenalin (II), on the other hand, yields *only* dihydroisohelenalin and the tetrasubstituted double bond is not reducible by the conventional catalytic methods. The results of ABU-SHADY and SOINE can be rationalized easily if we assume that their 'ambrosin' is actually a mixture of approximately 50% of XIII, for which we retain the name ambrosin and 50% of XIV, which we wish to call isoambrosin. This proposal is supported by the following experimental observations²: (a) The mixture of XIII and XIV described as ambrosin absorbs 1.41 mole equivalents of hydrogen yielding XV and XVI. (b) The infrared spectrum has bands at 1770 cm^{-1} (γ -lactone); $1718, 1594, 815\text{ cm}^{-1}$ (alkylcyclopentenone); 1675 cm^{-1} (tetrasubstituted double bond of γ -lactone); $1650, 910\text{ cm}^{-1}$ (conjugated $\text{CH}_2=\text{CR}_2$). (c) The high extinction in the ultraviolet spectrum ($\epsilon\ 13465$) observed is in agreement with our suggestion because the cisoid helenalin (I) has $\epsilon\ 12200$ whereby the transoid isohelenalin (II) has $\epsilon\ 20000$. (d) On ozonization the mixture yielded 35% of the theoretical amount (50%) of formaldehyde. (e) 'Ambrosin', like helenalin (I)¹¹, forms a monopiperonylidene derivative which is probably XX.

Similarly we would like to suggest that 'damsin' is a 1:1 mixture of XVII and dihydroisoambrosin (XVI). The following evidence² seems to support this proposal. (a) Catalytic reduction of the compound described as 'damsin' is complete after the uptake of 0.47 mole equivalents of hydrogen. (b) The dihydroisoambrosin (XVI) present in the mixture remains unchanged while damsine itself (XVII) is reduced to tetrahydroambrosin (XV). (c) The infrared spectrum of the mixture of XVI and XVII has bands at $1754\text{--}1766\text{ cm}^{-1}$ (broad) (γ -lactone and cyclopentanone); 1677 cm^{-1} (tetrasubstituted double bond of γ -lactone); $1650, 910\text{ cm}^{-1}$ (conjugated $\text{CH}_2=\text{CR}_2$). (d) Damsin gives a negative Tollens test. (e) Ozonization of the mixture of isomers gave 33% of the theoretical amount (50%) of formaldehyde. We may

further conclude that 'dihydroambrosin' is actually dihydroisoambrosin (XVI) and its infrared spectrum with bands at 1750 cm^{-1} (broad) (γ -lactone and cyclopentanone); 1672 cm^{-1} (strong) (tetrasubstituted double bond of γ -lactone) is in agreement with this formulation. The



'dihydroambrosinol' described previously² must thus be XVIII and the dicarboxylic acid obtained by nitric acid oxidation of XVI can now be formulated as XIX. The infrared spectra of these compounds are in good agreement with the postulated structures. These arguments further suggest expression XV for tetrahydroambrosin (1764 cm^{-1} ; γ -lactone; 1745 cm^{-1} ; cyclopentanone) the common reduction product of XIII and XVII. It is of interest to mention that the wavelength of infrared absorption of the carbonyl band of γ -lactones is not materially affected by conjugation with the cisoid methylene group. This fact had been noted before with

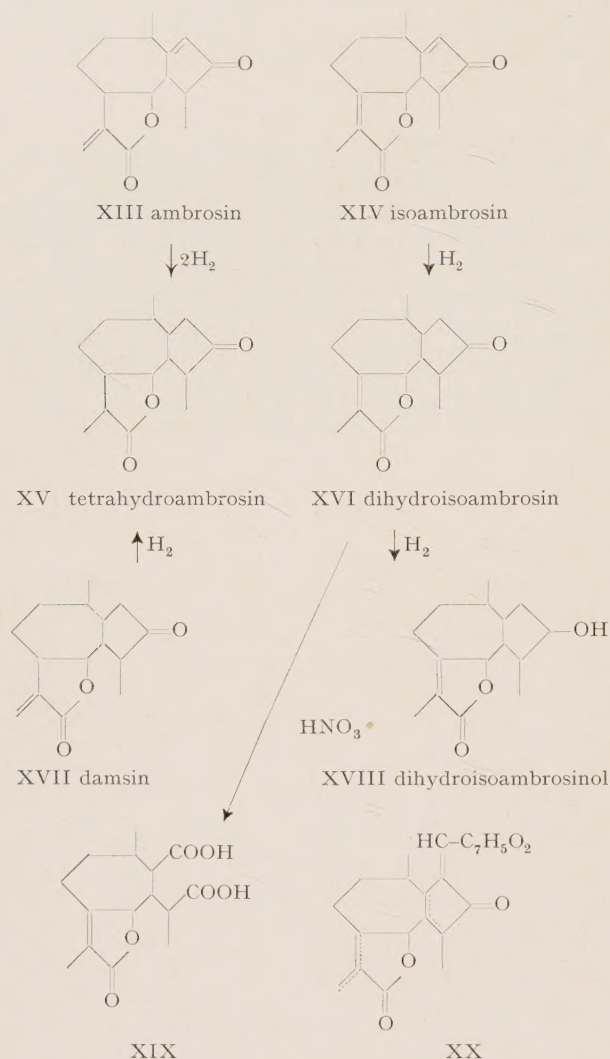
⁸ Isolated from *Helenium microcephalum*. – G. BÜCHI, L. BERNARDI, and D. ROSENTHAL (unpublished).

⁹ G. BÜCHI, L. BERNARDI, and D. ROSENTHAL (unpublished).

¹⁰ G. BÜCHI and D. ROSENTHAL, J. Amer. chem. Soc. 78, 3860 (1956).

¹¹ R. ADAMS and W. HERZ, J. Amer. chem. Soc. 71, 2456, 2551, 2554 (1949).

helenalin (I)¹¹, pyrethrosin¹² and with five-ring ketones from garryine and veatchine¹³.



Finally, the Kuhn-Roth C-methyl values of 'ambrosin', 'damsine', dihydroisoambrosin and tetrahydroambrosin are in good agreement with the values reported¹¹ for the corresponding helenalin derivatives.

We are indebted to Firmenich and Co., Geneva for a fellowship to L.B.

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Department of Chemistry, Massachusetts Institute of Technology, Cambridge, U.S.A., May 16, 1957.

Zusammenfassung

Es wird gezeigt, dass die von ABU-SHADY und SOINE isolierten Sesquiterpenlaktone «Ambrosin» und «Damsine» vermutlich Gemische von isomeren Substanzen darstellen. Die Interpretation bereits bekannter Tatsachen über die beiden Naturstoffe und der Vergleich mit verwandten Produkten ermöglicht die Aufstellung provisorischer Strukturformeln.

¹² D. H. R. BARTON and P. DE MAYO, J. chem. Soc. 1957, 150.

¹³ K. WIESNER, R. AMSTRONG, M. F. BARTLETT, and J. A. EDWARDS, J. Amer. chem. Soc. 76, 6068 (1954).

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Voacamidin und Voacristin, zwei neue Alkaloide aus *Voacanga africana* Stapf

Aus der in Afrika heimischen Apocynacee *Voacanga africana* Stapf sind bis jetzt durch Chromatographie der Gesamtalkaloide an Al_2O_3 folgende Inhaltsstoffe isoliert worden: Voacangin¹, Voacamin² (= Voacanginin³), Voacaminin⁴, Vobtusin⁵ und Voacarin⁶ (= Voacalin⁷?). Die Alkaloide sind Derivate des Indols bzw. 5-Methoxyindols; mit Ausnahme des Voacangins enthalten sie zwei Indolkerne.

Wir haben aus *Voacanga africana* Stapf zwei weitere neue Alkaloide in reiner Form isoliert, für die wir die Namen Voacamidin und Voacristin vorschlagen.

Voacamidin wurde auf Grund seiner etwas stärkeren Basizität durch Anwendung des Verteilungsverfahrens nach CRAIG von Voacamin und auf Grund der Schwerlöslichkeit seiner halogenwasserstoffsäuren Salze von Voacristin abgetrennt.

Die Base ist nach ihrem Verhalten bei der Craig-Verteilung sowie bei der Papierchromatographie einheitlich; ihre Kristallisationstendenz ist sehr gering. Sie kristallisierte jedoch aus Benzol in farblosen Nadeln; Smp. 128–130° (Zers.); $[\alpha]_D^{25} = -174,5^\circ$ (Chloroform); Summenformel $\text{C}_{45}\text{H}_{56}\text{O}_6\text{N}_4$ (ber.: C 72,16; H 7,54; N 7,48; 3 $-\text{OCH}_3$ 9,26; $>\text{NCH}_3$ 1,49%; gef.: C 72,10; H 7,56; N 7,79; $-\text{OCH}_3$ 9,56; 9,56; 9,41; $>\text{NCH}_3$ 2,19; 1,49%).

Das UV.-Spektrum in Methanol hat charakteristische Maxima bei 227,5 μ ($\log \epsilon$ 4,74) und bei 292,5 μ ($\log \epsilon$ 4,32), die einer 5-Methoxyindol-Gruppierung entsprechen. Das in Chloroform gemessene IR.-Spektrum enthält Banden bei 2,79 (OH); 2,91 (NH), 5,85 (CO), 6,20 und 6,37 μ (C=C). Weitere starke Banden (fest in KBr gemessen) finden sich bei 13,56 μ und bei 14,8 μ (OH?). Voacamidin ist demnach isomer mit Voacamin; seine spektralen Eigenschaften sind denen des Voacamins sehr ähnlich.

Hydrochlorid. Aus Aceton/Methanol farblose Nadeln; Smp. 265–267° (Zers.); $[\alpha]_D^{25} = -166,5^\circ$ (Methanol); $\text{C}_{45}\text{H}_{58}\text{O}_6\text{N}_4\text{Cl}_2$ (ber.: C 65,76; H 7,11; N 6,82; Cl 8,63%; gef.: C 65,64; 65,43; H 6,97; 6,86; N 6,81; 7,13; Cl 8,94%).

Hydrobromid. Aus Aceton farblose Nadeln; Smp. 265 bis 266° (Zers.); $[\alpha]_D^{25} = -144^\circ$ (Methanol); $\text{C}_{45}\text{H}_{58}\text{O}_6\text{N}_4\text{Br}_2 \cdot 1/2 \text{H}_2\text{O}$ (ber.: C 58,76; H 6,47; N 6,09%; gef.: C 58,65; 58,75; H 6,38; 6,52; N 6,83; 6,75%).

Hydrojodid. Aus Aceton farblose Nadeln; Smp. 263 bis 264° (Zers.); $[\alpha]_D^{25} = -142^\circ$ (Methanol). $\text{C}_{45}\text{H}_{58}\text{O}_6\text{N}_4\text{J}_2 \cdot 1/2 \text{H}_2\text{O}$ (ber.: C 53,31; H 5,87; N 5,53%; gef.: C 53,15; 53,22; H 5,96; 5,88; N 5,39%).

¹ M.-M. JANOT und R. GOUTARAL, C. r. Acad. Sci., Paris 240, 1800 (1955). – J. LA BARRE und L. GILLO, Bull. Acad. Méd. Belg. 20, 194 (1955).

² M.-M. JANOT und R. GOUTAREL, C. r. Acad. Sci., Paris 240, 1719 (1955). – R. GOUTAREL und M.-M. JANOT, C. r. Acad. Sci., Paris 242, 2981 (1956).

³ J. LA BARRE und L. GILLO, Bull. Acad. Méd. Belg. 20, 194 (1955).

⁴ J. LA BARRE, J. LEQUIME und J. VAN HEERSWYNHEL, Bull. Acad. Méd. Belg. 20, 415 (1955).

⁵ M.-M. JANOT und R. GOUTARAL, C. r. Acad. Sci., Paris 240, 1719 (1955).

⁶ R. GOUTAREL und M.-M. JANOT, C. r. Acad. Sci., Paris 242, 2981 (1956).

⁷ J. LA BARRE und L. GILLO, C. r. Soc. Biol., Paris 150, 1628 (1956).

Mit Pyridin-Acetanhydrid wurde aus Voacamidin ein *Acetylderivat* gewonnen, das als kristallisiertes Hydrobromid charakterisiert wurde: Aus Aceton/Methanol farblose Nadeln; Smp. 272–273° (Zers.) $[\alpha]_D^{20} = -148,8^\circ$ (Methanol). $C_{47}H_{60}O_7N_4Br_2$ (ber.: C 59,24; H 6,35; N 5,88%; gef.: C 59,25; 59,10; 59,35; H 6,24; 6,42; 6,55; N 5,82; 5,94%).

Behandlung des Voacamidins mit äthanolischer Kalilauge führte zum kristallisierten Kaliumsalz einer Säure, die in saurem Milieu bei etwa 80° decarboxylierte. Das Decarboxylierungsprodukt kristallisierte aus wässrigem Methanol in farblosen Nadeln; Smp. 239–240°. $C_{42}H_{52}O_4N_4$ (ber.: C 74,53; H 7,74; N 8,28%; gef.: C 74,66; 74,64; H 7,73; 7,75; N 8,34; 8,36%). Die Substanz enthält nur noch eine CH_3O -Gruppe (ber.: 1 OCH_3 4,58; gef.: 4,11; 4,45%). Bei der alkalischen Hydrolyse sind also zwei Methylestergruppierungen verseift worden. Eine der beiden Carboxylfunktionen wurde durch Decarboxylierung eliminiert; auch die andere liegt, wie aus dem nicht amphoter Charakter der Substanz und der Lage einer CO-Bande bei 5,84 μ geschlossen werden muss, nicht mehr als freie Carboxylgruppe vor. Voacamidin verhält sich nach diesen Befunden auch bei der alkalischen Verseifung ähnlich wie Voacamin⁸.

Voacristin, das zweite aus *Voacanga africana* Stapf isolierte neue Alkaloid, ist auf Grund seiner bei der Craig-Verteilung ermittelten Verteilungskurve einheitlich. Es kristallisierte aus 70prozentigem Methanol in farblosen Blättchen, Smp. 112–114°; $[\alpha]_D^{20} = -24,5^\circ$ (Chloroform). Die Elementaranalysen (gef.: C 69,01; 69,32; H 7,44; 7,57; N 7,19; 7,06%) lassen sich sowohl mit der Summenformel $C_{45}H_{58}O_8N_4$ (ber.: C 69,0; H 7,46; N 7,15%) als auch mit $C_{23}H_{30}O_4N_2$ (ber.: C 69,32; H 7,59; N 7,03%) in Einklang bringen.

Das UV.-Spektrum ist durch Maxima bei 225 und 285 $m\mu$

(E 1%/1cm = 636; 247)

charakterisiert; das IR.-Spektrum in Chloroform zeigt im kürzerwelligen Teil scharfe Banden bei 2,91 (NH) und 5,83 μ (CO); verbreiterte Banden bei 3,2–3,6 und 8,0 bis 8,4 μ ; im längerwelligen Teil (in KBr gemessen) tritt vor allem eine Gruppe von 3 Banden im Gebiet von 12 bis 13 μ sowie eine Bande bei 14,8 μ in Erscheinung.

Acetylderivat. Aus Methanol Nadeln vom Smp. 187 bis 188°. Die Analysenwerte (gef.: C 68,13; 68,32; H 7,38; 7,47; N 6,32; 6,42) stimmen auf die Formeln $C_{51}H_{66}O_{10}N_4$ (ber.: C 68,43; H 7,43; N 6,26%) oder $C_{25}H_{32}O_5N_2$ (ber.: C 68,16; H 7,32; N 6,36%).

Mit weiteren Versuchen zur Konstitutionsaufklärung der beiden Alkaloide sind wir beschäftigt.

U. RENNER

Wissenschaftliche Abteilung der Dr. Karl Thomae G.m.b.H., Biberach an der Riss und Forschungsabteilung der J. R. Geigy A.G., Basel, 8. Juli 1957.

Summary

From the bark and the root-bark of *Voacanga africana* Stapf, two new alkaloids have been isolated and characterized.

⁸ R. GOUTAREL, F. PERCHERON und M.-M. JANOT, C. r. Acad. Sci., Paris 243, 1670 (1956).

Künstliche Niere mit Kapillarsystem für den Stoffaustausch¹

Der Zweck einer künstlichen Niere besteht darin, harnpflichtige Substanzen und gegebenenfalls auch Wasser aus dem Blut bzw. aus dem Organismus herauszunehmen. Dies geschieht dadurch, dass man das Blut auf der einen, eine Dialysierlösung auf der anderen Seite einer und derselben Membran vorbeiströmen lässt. Bei geeigneter Porengrösse ist die Membran für Eiweissmoleküle undurchlässig, für die niedrigmolekularen Stoffe wie Salze, Wasser und harnpflichtige Substanzen dagegen durchlässig.

In der nachfolgenden Mitteilung wird gezeigt, dass es möglich ist, der Dialysierlösung eine solche Zusammensetzung zu geben, dass zwischen Blut und Dialysierlösung Gleichgewicht sowohl hinsichtlich der Salze als auch hinsichtlich Wasser besteht, so dass dem Blut ohne Verlust an Eiweiss, Salzen und Wasser die harnpflichtigen Substanzen entzogen werden können. In diesem Falle erfolgt die Entfernung der harnpflichtigen Substanzen aus dem Blut durch Diffusion der zu entfernen Stoffe durch die Membran aus dem Blut in die Dialysierlösung. Theoretische und experimentelle Untersuchungen über den Stoffaustausch zwischen strömenden Flüssigkeiten durch eine die Flüssigkeiten trennende Membran zeigen, dass der Stoffübertritt pro Flächeneinheit der Membran einmal um so ausgiebiger ist, je dünner die Membran ist, dass aber ausserdem die Dicke der zu beiden Seiten der Membran entlang strömenden Flüssigkeitsschichten, das heisst die Tiefe der Kanäle, von grosser Bedeutung ist. Wenn die Kanäle tief sind, bleibt bei gegebener, pro Zeiteinheit durchströmender Menge an Blut bzw. an Dialysierlösung im betreffenden Kanal eine Flüssigkeitsschicht beträchtlicher Dicke praktisch genommen in Ruhe, und die unbewegte Schicht trägt zur Behinderung des Stoffaustauschs zwischen den nahe der Kanalmitte strömenden Flüssigkeitsteilen bei. Auf Grund dieser Feststellungen und Überlegungen wird der pro Zeiteinheit und pro Flächeneinheit der Membran zu erzielende Stoffaustausch hinaufgesetzt, wenn eine sehr dünne, zum Beispiel eine $1/100$ mm dicke Membran verwendet wird und gleichzeitig die Tiefe der das Blut und die Dialysierlösung an der Membran vorbeiführenden Kanäle sehr niedrig gehalten wird. Da mit der Herabsetzung des Querschnitts des einzelnen Flüssigkeitskanals der Poiseuill'sche Strömungswiderstand anwächst, ist es, um einen genügenden Durchsatz zu erzielen, notwendig, anstatt eines einzigen sehr langen eine Vielzahl parallel geschalteter enger Kanäle sowohl für das Blut als auch für die Dialysierlösung zu verwenden. Das heisst, man wird dazu geführt, für den Stoffaustausch in der künstlichen Niere ein Kapillarsystem zu verwenden.

Ein unter diesen Gesichtspunkten aufgebauter Dialysator ist in Abbildung 1a und 1b dargestellt. In zwei spiegelbildlich bearbeitete Plexiglasplatten ist ein in sich zusammenhängendes Kapillarsystem eingeschnitten. Zwischen die beiden Platten (P_1 und P_2 in Abb. 2) bringt man zwei Zellophanfolien F_1 , F_2 von je $1/100$ mm Dicke. An allen Stellen S_1 , S_2 , an denen sich bei den Platten Stege befinden, werden die Folien fest aufeinandergepresst, während sie an den Stellen, an denen die Plexiglasplatten die Rillen R_1 , R_2 tragen, frei liegen (Abb. 1a).

¹ Vorgetragen am Kongress der «3° riunione medico chirurgica internazionale», Turin 1957.

Leitet man nun mittels eines speziellen Zuführungssystems an einer Stelle Z des mittleren Ringkanals M (Abb. 1a) Blut zwischen die beiden Folien ein, so bauchen sich diese auf und begrenzen einen Kanal mit linsenförmigem Querschnitt. Aus dem mittleren Ringkanal (M in Abb. 1a) gelangt das Blut, immer zwischen den beiden Zellophanfolien fließend, weiter in die nach innen und aussen führenden Radialkanäle K (Abb. 1a),

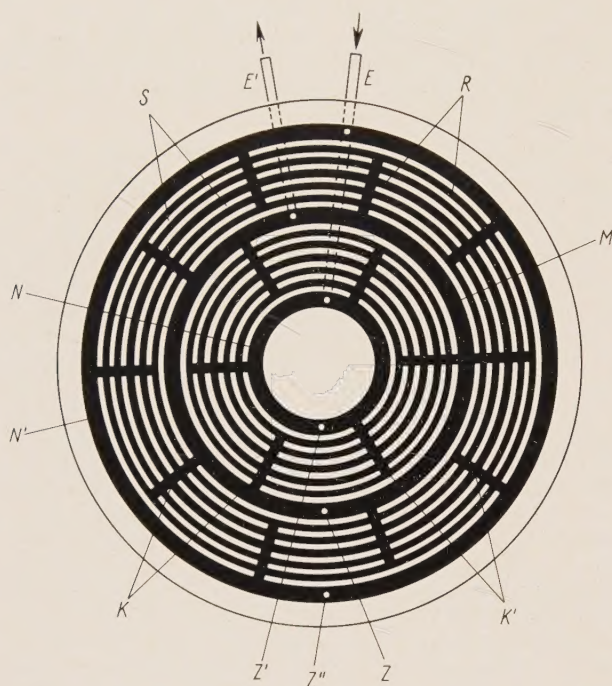


Abb. 1a. Kapillarsystem für den Stoffaustausch, Aufsicht, schematisch:

- Z Sonde zur Zuführung des Blutes in den von zwei Zellophanfolien gebildeten Kanal von linsenförmigem Querschnitt (siehe F_1, F_2 in Abb. 2b);
 Z', Z'' Sonden zur Wegführung des Blutes;
 E, E' Sonden zur Zu- und Wegführung der Dialysierlösung;
 K, K' Radialkanäle;
 R Rillen (siehe Abb. 2);
 S Stege
 M mittlerer Ringkanal;
 N, N' innerer und äusserer Ringkanal.

an welche sich die konzentrisch angeordneten, parallelgeschalteten eigentlichen Austauschkanäle R (Abb. 1a) anschliessen. Im ganzen Bereich des in Abbildung 1a angedeuteten Kanalnetzes fliesst das Blut, wie bereits bemerkt, zwischen zwei Zellophanfolien, welche in der in Abbildung 2b angedeuteten Weise von Dialysierlösung gespült werden. Zum Schluss führen ähnliche Radialkanäle K' das Blut dem innern bzw. äusseren Ringkanal N bzw. N' (Abb. 1a) zu, von wo es bei Z' bzw. Z'' (Abb. 1a) den Dialysator verlässt. Die Dialysierlösung ihrerseits fliesst in den in die Plexiglasplatten geschnittenen Rillen (R_1 und R_2 in Abb. 2) an beiden Membranen vorbei, und zwar im Gegenstrom zum Blut. Man erreicht durch diese Anordnung nicht nur eine Verdoppelung der wirksamen Membranaustauschfläche, sondern verhindert auch, dass das Blut mit dem Plexiglas in Berührung kommt.

Insgesamt sind in dem in Abbildung 1b in $1/5$ natürlicher Grösse dargestellten Dialysatorelement etwa 2000 parallel geschaltete Austauschkanälchen untergebracht, von denen jedes eine Breite von 1 mm und eine mittlere

Länge von 1,8 cm besitzt. Die Dicke der Blutschicht und der Dialysierlösungsschichten beträgt etwa $3/100$ mm, die für den Austausch wirksame Membranfläche 700 cm^2 und das zur Füllung des Dialysatorelements benötigte Blutvolumen 5 cm^3 .

Den Transport des Blutes im Dialysator besorgt eine speziell entwickelte Membranpumpe, welche mit Klappenventilen ausgerüstet ist. Die Ventilklappen bestehen aus

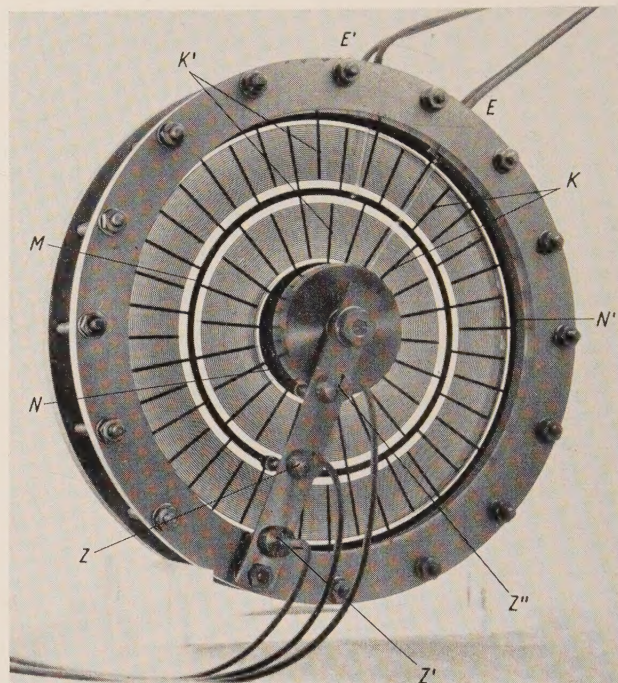


Abb. 1b. Dialysator mit Kapillarsystem für den Stoffaustausch. Gesamtansicht in $1/5$ natürlicher Grösse. Die in der Abbildung eingetragenen Buchstaben haben dieselbe Bedeutung wie in Abbildung 1a.

synthetischen wässrigen Gelen, deren Oberfläche so weich ist, dass die beim Rückschlag eingeklemmten Blutkörperchen nicht zerdrückt werden, sondern sich in das Gelmaterial einpressen können. Auf diese Weise lässt sich eine Hämolyse praktisch ausschalten.

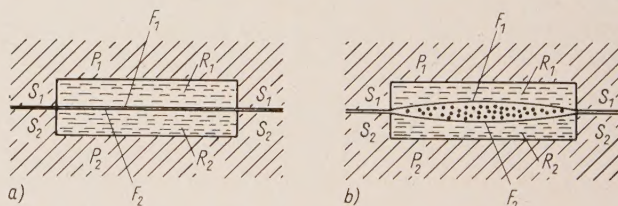


Abb. 2. Querschnitt durch die von Plexiglas und Dialysierfolien begrenzten Kanäle für Blut und Dialysierlösung:

- P_1, P_2 erste und zweite Plexiglasplatte;
 S_1, S_2 Stege an den Platten P_1 bzw. P_2 ;
 R_1, R_2 Rillen an den Platten P_1 bzw. P_2 ;
 F_1, F_2 erste und zweite Dialysierfolie.

Das Blut wird an passender Stelle zwischen die Dialysierfolien F_1 und F_2 eingeleitet. Bei fehlendem Überdruck des Blutes berühren sich die Folien F_1 und F_2 unmittelbar (Abb. 2a). Bei Anwendung eines kleinen Überdruckes des zwischen die Folien eingeleiteten Blutes bildet sich durch Ausbauchung der Folien ein Kanal mit linsenförmigem Querschnitt (F_1, F_2 in Abb. 2b).

Der Dialysator wurde bereits in Laborversuchen getestet. Aus den erhaltenen Resultaten ergibt sich, dass bei Verwendung von vier der beschriebenen Dialy-

satorelemente in Parallelschaltung, was einer Austauschfläche von insgesamt 2800 cm^2 entspricht, bei einem Durchsatz von 14 l/h der Gehalt des Organismus an harnpflichtigen Substanzen eines 75 kg schweren Patienten durch 9stündige Dialyse auf 40% des Anfangswertes herabgesetzt werden kann; das entspricht einer Clearance von 80 ml/min . Das Volumen des dabei zu verwendenden Dialysatorsystems einschliesslich Pumpe und Schlauchzuleitungen beträgt nur etwa 100 cm^3 . Die Aufenthaltszeit des Blutes im gesamten System beläuft sich auf etwa 30 s , in den eigentlichen Dialysierkanälen auf 1 s .

Die Unterzeichneten danken der Fritz-Hoffmann-La-Roche-Stiftung zur Förderung wissenschaftlicher Arbeitsgemeinschaften für die Mittel, die sie für diese Arbeiten zur Verfügung gestellt hat.

W. KUHN, H. MAJER,
H. HEUSSER und B. ZEN RUFFINEN

Aus dem Physikalisch-Chemischen Institut der Universität Basel und der II. Chirurgischen Abteilung des Bürgerspitals Basel, 1. August 1957.

Summary

A particularly efficient removal of urea and similar substances by dialysis in an artificial kidney is obtained if both blood and dialyzing liquid are allowed to flow in countercurrent through channels a few hundredths of a mm thick and separated from each other by a membrane about $\frac{1}{100}$ of a mm thick. In order practically to realize the flow required, about two thousand of these narrow channels, each of a length of about 2 cm , are arranged parallel to form a capillary net system.

Four elements, each consisting of 2000 narrow channels, are needed in order to obtain a clearance of 80 ml/min . The quantity of blood needed to fill the elements is about 5 cm^3 for each element.

Regulierung des Wasserhaushaltes bei der Hämodialyse (Kompensation und Überkompensation des kolloidosmotischen Druckes des Blutes durch Verwendung polyelektrolythaltiger Dialysierlösungen bei der künstlichen Niere)¹

Das bei Anwendung einer künstlichen Niere verfolgte Ziel ist in erster Linie und bekanntlich die Entfernung der harnpflichtigen Substanzen. Wichtig ist es, dass dabei einerseits kein Verlust des Organismus an Eiweiss oder Salzen auftritt, dass aber auch andererseits keine Überführung von Wasser aus der Dialysierlösung in das Blut stattfindet. Es zeigt sich, dass bei Verwendung einer geeigneten Dialysierlösung diese Forderungen erfüllt werden können und dass man darüber hinaus sogar die Möglichkeit erhält, dem Blute, ohne den Haushalt hinsichtlich Salzen und Eiweiss zu stören, beträchtliche Mengen an Wasser zu entziehen. Das letztere dürfte beim Vorliegen von Ödemen von praktischer Bedeutung sein.

¹ Vorgetragen am Kongress der «3° riunione medico chirurgica internazionale», Turin 1957; erste Mitteilung hierüber im Vortrag von W. KUHN am Staffmeeting des Bürgerspitals Basel am 2. Februar 1955.

Ein Verlust an Eiweisssubstanzen kann bekanntlich durch Verwendung einer Membran geeigneter Porengrösse verhindert werden. Bei Verwendung einer solchen Membran treten die niedermolekularen Verbindungen wie Salze, harnpflichtige Stoffe und Wasser in jeder Richtung durch die Membran hindurch, während die grossen Eiweissmoleküle zurückgehalten werden. Es wird damit eine Entfernung der harnpflichtigen Stoffe ohne Beeinflussung des Eiweissgehaltes des Blutes ermöglicht.

Dagegen führt die gleichzeitige Durchlässigkeit der Membran für Wasser und Salze andererseits zunächst zu einer unbefriedigenden Lage hinsichtlich des Wasser- und Salzhaushaltes. Verwendet man nämlich eine Dialysierlösung, welche hinsichtlich des Salzgehaltes mit dem Blut im Gleichgewicht steht, so ergibt sich eine Schwierigkeit für den Wasserhaushalt, indem im Falle des Blutes zu dem von den Salzen herrührenden osmotischen Druck der von den Kolloiden herrührende kolloidosmotische Druck von ungefähr 40 cm Wassersäule hinzutritt. Bei Äquivalenz der Salzkonzentration in Blut und Dialysierlösung hat das Blut den grösseren osmotischen Druck. Es zieht durch die Membran Wasser aus der Dialysierlösung an und wird dadurch verwässert.

Eine Kompensation des kolloidosmotischen Druckes des Blutes, das heisst eine Korrektur des Wasserhaushaltes, würde sich durch Erhöhung der Salzkonzentration in der Dialysierlösung erreichen lassen. Dies ist aber nicht statthaft, weil, sobald die Dialysierlösung eine höhere Salzkonzentration als das Blut besitzt, Salz durch die Membran ins Blut übertritt, so dass das Blut eine Versalzung erleidet. Das Blut wird also verwässert oder versalzen, je nachdem der Salzgehalt der Dialysierlösung dem Salzgehalt oder dem gesamtosmotischen Druck des Blutes angepasst wird.

Es zeigt sich nun, dass eine Kompensation oder sogar Überkompensation des kolloidosmotischen Druckes unter gleichzeitiger genauer Erhaltung des Gleichgewichtes hinsichtlich der vorhandenen Salze dadurch gelingt, dass man der Dialysierlösung einen Polyelektrolyten zusetzt. Ein Polyelektrolyt ist eine Substanz, welche ein hohes Molekulargewicht besitzt und demzufolge nicht durch die Membran hindurchtreten kann, welche aber trotzdem infolge der elektrolytischen Dissoziation einen grossen osmotischen Druck erzeugt. Als günstig erwies sich die Carboxymethylzellulose; unter anderem zeigte sich, dass diese Substanz nicht toxisch ist und selbst bei massiven intravenösen Gaben weder bei Ratten, Kaninchen oder Hunden Früh- oder Spätschäden hervorruft.

Fügt man Carboxymethylzellulose, deren Molekulargewicht so hoch gewählt wird, dass sie nicht durch die Membran hindurchtreten kann, neben den Salzen in der richtigen Konzentration zur Dialysierlösung hinzu, so sind alle Blutkomponenten ausser den harnpflichtigen Substanzen abkompensiert, und ausser deren Übertritt in die Dialysierlösung findet kein anderer Austauschprozess statt; das heisst, das Blut bleibt bezüglich der übrigen Komponenten in seiner Zusammensetzung ungeändert.

Durch passende Erhöhung der Konzentration der Carboxymethylzellulose ergibt sich, wie angedeutet, sogar die Möglichkeit, eine Überkompensation des kolloidosmotischen Druckes des Blutes zu erreichen. Eine solche Erhöhung des osmotischen Druckes der Dialysierlösung über den dem Blute zukommenden osmotischen Druck kann dazu benützt werden, dem Blut Wasser zu entziehen, und zwar ohne dass dabei, wie es bei Anwen-

dung eines hydrostatischen Druckes der Fall wäre, die Membran mechanisch beansprucht wird.

Beispielsweise weist eine Dialysierlösung, welche neben den Salzen 4% einer Carboxymethylzellulose vom mittleren Molekulargewicht 12000 enthält, einen osmotischen Druck von etwa 2–3 m Wassersäule auf. Mit Hilfe dieses Druckes lassen sich dann bei Verwendung des in der vorhergehenden Mitteilung beschriebenen Dialysators pro Stunde etwa 400 ml Wasser aus dem Organismus eines Patienten entziehen.

Die Unterzeichneten danken der Fritz-Hoffmann-La-Roche-Stiftung zur Förderung wissenschaftlicher Arbeitsgemeinschaften für die Mittel, die sie für diese Arbeiten zur Verfügung gestellt hat.

W. KUHN, H. MAJER,
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Aus dem Physikalisch-Chemischen Institut der Universität Basel und der II. Chirurgischen Abteilung des Bürgerspitals Basel, 1. August 1957.

Summary

Addition of polyelectrolytes, in particular of the sodium salt of carboxymethylcellulose, makes it possible to obtain for the use in artificial kidneys dialyzing liquids which are in thermodynamic equilibrium with blood, both with respect to salts and water, or which even permit removal of water from the blood, as well as urea and related substances (the dialyzing liquid being at will hypertonic with respect to blood), the salt content of blood remaining in all these cases unaffected. These dialyzing liquids might be particularly useful for cases combined with oedema.

A Fluid Drop Model of the Elliptical Red Blood Cell

Current studies in this laboratory are concerned with the occurrence and significance of form differences between homologous cells of polyploid animals. Especially interesting are the alterations in form of the red cells of the salamander, *Triturus viridescens*.

Triploid larvae (3–4 finger stage) were obtained and identified according to FANKHAUSER¹. The elliptical areas of the fresh red cells were traced on standard weight cards with the camera lucida. The areas of the cells were determined from the proportional weights and recorded together with the ratio of the major to minor semi-axes (a/b) as an index of the eccentricity of the elliptical cells. It is evident from the Table that the areas of triploid blood cells are almost exactly 1.5 times greater than those of diploid controls, a fact consistent with the view that the cell thickness has remained the same. A similar situation has been reported by FANKHAUSER for epidermal cell nuclei which also remain of constant thickness¹. In addition to the differences in area there are obvious differences in the eccentricities of the cells ($a/b = 1.55$ in the diploids and 1.82 in the triploids). Employing the property that $x^2/a^2 + y^2/b^2 = 1$, it is possible to construct the mean form of the cells in Figure 1.

The blood cell exists in a system of cylinders, the blood vessels. The many similarities between protoplasmic structures and fluid drops have long been appreciated². These considerations suggest an examination of the

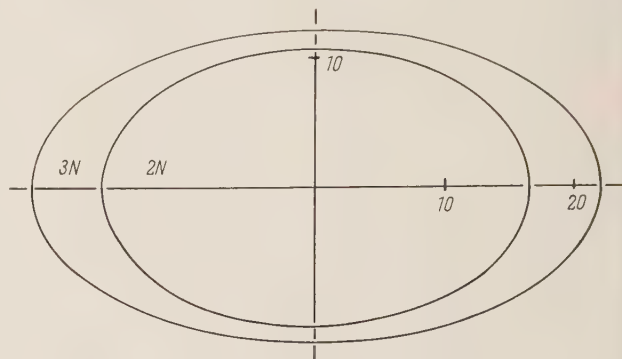


Fig. 1.—The mean forms of triploid and diploid blood cells. The ellipses were constructed on coordinate paper from the measured areas and eccentricities employing the property that $x^2/a^2 + y^2/b^2 = 1$. The coordinates are in microns.

form assumed by fluid drops in contact with a cylindrical surface. In order to obtain a fluid drop of mercury approximating the blood cell in relative dimensions, it is necessary to employ a very large glass cylinder (290 mm in diameter) placed with the axis horizontal. After introducing a known weight of mercury, the cylinder can be tipped and levelled to bring the drop to rest over a coordinate system of millimeter graph paper cemented to the outer surface of the cylinder. The major and minor axes of the drop are then measured by means of the graph paper. The eccentricity (a/b) and area (πab) are determined. Knowing the weight and hence the volume of the introduced mercury, the average thickness may be calculated assuming the drop to be a flat elliptical cylinder of thickness d and volume πabd . Both eccentricity (a/b) and thickness (d) are plotted against drop area in Figure 2. Eccentricity steadily increases while thickness increases only slightly (2%) over the range of eccentricities characteristic of the blood cells. A 'diploid' drop with an eccentricity of 1.55 has an area of 740 mm². A 'triploid' drop (1.5 times greater volume has an area of 1080 mm² and an eccentricity of 1.89 a value comparable to 1.82 for the triploid blood cell. The ratio of areas is also very similar being 1.49/1 for the cell and 1.47/1 for the mercury model.

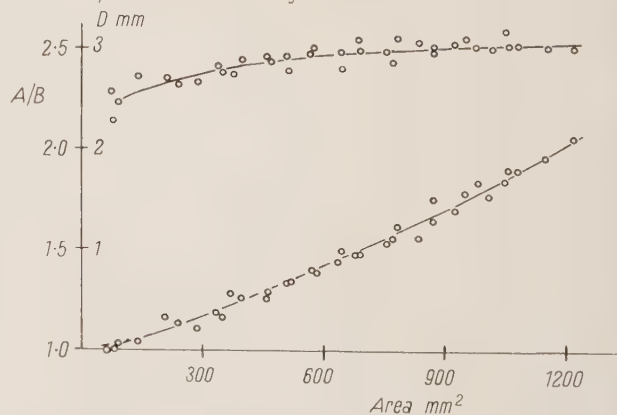


Fig. 2.—The form assumed by mercury drops in a glass cylinder. a/b (lower points and left ordinate) and calculated thickness d (upper points and right ordinate) plotted versus area of the ellipse (abscissa). Inside diameter of the cylinder = 290 mm. Temperature = about 20°C.

¹ G. FANKHAUSER, *Int. Rev. Cytol.* 1, 165 (1952).

² THOMPSON, D'ARCY, *On Growth and Form* (Cambridge 1942).

The use of the model as an explanation of the red cell form requires that the red cell be in contact with a cylindrical surface as is the mercury drop. While passing through the gill capillaries one elliptical surface of the red cell is usually applied to the capillary wall although this is not the case in larger blood vessels. It is also required that capillary diameter be no greater in triploids since, other factors remaining constant, the larger the diameter of the cylinder the less eccentric will be the fluid drop. Measurements of gill capillary diameters disclosed no differences between diploids and triploids. FANKHAUSER reports constant diameter for another tubular structure, the kidney tubule¹.

The model lacks the bulging nucleus characteristic of the amphibian red cell. However, salamanders of the genus *Batrachoseps* are characterized by anucleate blood cells (erythroplastids) formed by cytoplasmic division from circulating nucleated erythrocytes³. As EMMEL's figures show, these blood elements are clearly elliptical in form with larger cells tending to be more eccentric but no greater in thickness. The presence of a nucleus does not alter the basic similarity between red cell form and the equilibrium form assumed by a fluid drop in contact with a cylindrical surface.

No. of Cells	$\frac{2n}{42}$	$\frac{3n}{40}$
Area/cell μ^2	$560 \pm 102^*$	843 ± 123
Eccent. a/b	1.55 ± 0.17	1.82 ± 0.21
	Area $3n = 1.49$	
	Area $2n = 1$	

* S.D. = $[S(\text{dev})^2/N]^{\frac{1}{2}}$

By maintaining the cell thickness constant the oxygen exchanging properties of the red cell undergo little change with increased cell volume. As already noted skin epidermis as well as lens epidermis remain of constant thickness. Considered as a diffusion barrier the properties of the epidermis are probably not altered by polyploidy. Similar considerations apply to the kidney tubule which remains constant in diameter and wall thickness. Stated in general terms: *cell dimensions perpendicular to physiological surfaces remain unaltered*. Consequently, the physiological properties of the polyploid animals themselves probably undergo little if any change.

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Division of Physiology, Department of Biological Sciences, Florida State University, Tallahassee, June 13, 1957.

Zusammenfassung

Der Flächeninhalt der elliptischen Erythrozyten des triploiden *Triturus viridescens* ist bei gleichbleibender Dicke der Zellen ungefähr 50% grösser als bei diploiden Kontrolltieren. Als Ellipse betrachtet, zeigt die triploide Zelle eine grössere Exzentrizität als die diploide. Im Kontakt mit der Wand eines horizontal gelagerten Zylinders vergrössert sich die Exzentrizität elliptischer Quecksilbertropfen mit zunehmendem Volumen; sie gleichen den Blutkörperchen auch insofern, als ihre

Dicke weitgehend konstant bleibt. Diese Beobachtungen unterstützen unsere Ansicht, wonach die endgültige Form der Erythrozyten weitgehend durch die physikalischen Kräfte bestimmt wird, welche während ihrer Reifung in den zylindrischen Blutgefässen, vor allem in den Kapillaren, wirksam sind.

Evidences for the Bipartite or Diploid Nuclei in Conidia of *Streptomyces griseoflavus*

Two kinds of mycelia, primary and secondary, are known in the life cycle of *Streptomyces fungi*¹. In 1947, KLIENBERGER-NOBEL proposed in her study of strains of *Actinomyces* that the primary mycelium might correspond to the haploid and the secondary to the diploid phase of her strains. But, owing to the technical limitation of studying such minute organisms by cytological means, conclusive evidences were not presented for the state of ploidy in the mycelia or in the conidia. In our study, the conidia of one strain of *Streptomyces griseoflavus* proved to be apparently uninucleate, but the nucleus seemed to be bipartite or diploid.

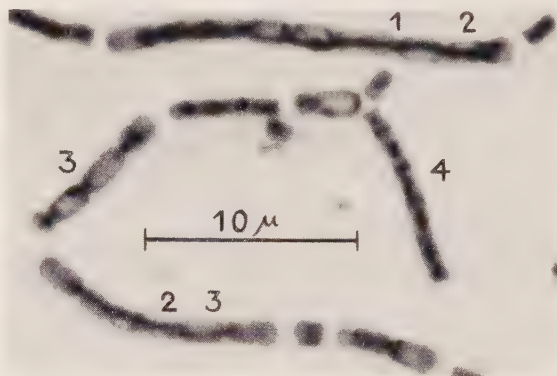


Fig. 1. A late stage of conidia formation in the order 1 to 4.

For cytological study, the strain was cultivated on a modified Krainsky's medium, supplemented with 0.25% yeast extract and 1% peptone, and the nuclei were stained by Robinow's technique. After 24 h at 30°, so-called initial cells (corresponding to the nest-like structure in KLIENBERGER-NOBEL's paper) were distinctly observed under a microscope. When the secondary mycelia developed from the initial cells, the behaviour of nuclei in the mycelia was as follows: at the beginning the chromatinic substances were fragmented, but later, they turned into threads or slender dumbbell forms and finally into thick rods. Upon spore formation, the rod-shaped substances divided into smaller parts so that every conidium was charged with two units. The figure soon after the segmentation is twisted and dumbbell-like; occasionally, figures are apparently showing two stainable bodies (Fig. 1). As time passes, the spheres of the dumbbell unite and, after maturation, only one nucleus is found in each conidium (Fig. 2).

¹ E. KLIENBERGER-NOBEL, J. gen. Microbiol. 1, 22 (1947). – J. F. MCGREGOR, J. gen. Microbiol. 11, 52 (1954).

³ V. E. EMMEL, Amer. J. Anat. 33, 347 (1924).

X-ray inactivation tests of the mature conidia gave 'two-hit' curves. With the assurance that more than 90% of the conidia were single, a saline solution containing about 10^6 of conidia per ml was exposed to X-rays (200 kV, 20 mA, filtered through a 1 mm aluminium plate) at a distance of 18 cm (1000 r/min). The frequency of survivors after irradiation was determined by routine methods. As the examples in Figure 3 show, survival



Fig. 2. — Mature conidia.

curves having a shoulder resulted. In a series of experiments with other mutants of the strain, the extrapolations were found to intercept the ordinate around 2.0 with a deviation of 0.3. In parallel, other species of *Streptomyces* were exposed to X-rays; *S. griseus* and *S. kitasatoensis* showed 'one-hit' curves.

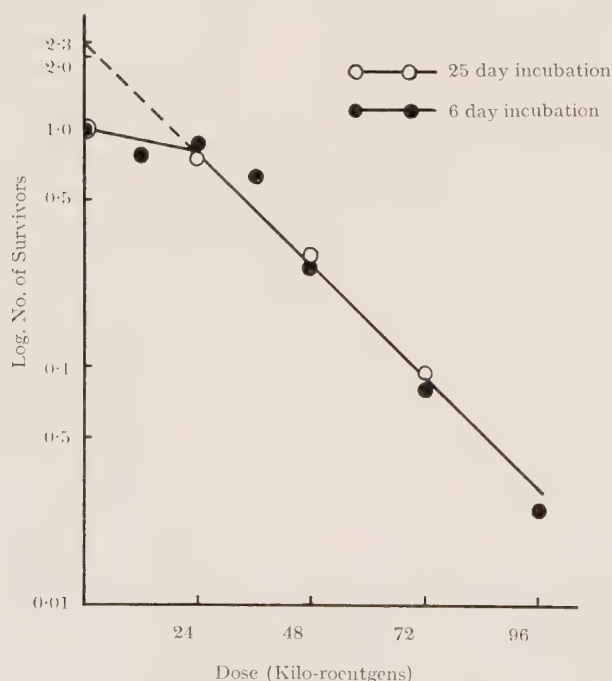


Fig. 3. — Survival of conidia after X-irradiation

In an attempt to isolate biochemical mutants among the conidia irradiated by ultraviolet light, we happened to gain another evidence supporting our view. When U. V. irradiated conidia were incubated in minimal medium and subsequently filtered through a glass filter,

the frequency of mutants among the colonies on complete medium was about 0.1%. However, if conidia were preincubated on complete medium for a week before letting the newly formed conidia stand in minimal medium, the frequency rose to 1%. These results are readily understandable if the nuclei in the conidia are bipartite or diploid, because the preincubation on complete medium would be favorable for the induced heterozygous nuclei to segregate out their components, the biochemical mutants.

In order to test the hypothesis more extensively, the following experiments were performed. By the use of a mutant requiring glutamate and methionine for growth, the segregation pattern of its reversions was studied in detail. First, a suspension of conidia was irradiated with a 15 watt germicidal lamp at a distance of 40 cm, and then was plated on methionine-supplemented agar. As a result, the frequency of back mutation among survivors with regard to glutamate dependence was found to be 10^{-7} at zero time and 10^{-5} after 2-min-irradiation (about 1% surviving). When the colonies became large, hundreds of conidia were carefully picked up from each colony and streaked on complete medium in order to examine the requirement of the resulting colonies by the replica technique. Out of 18 back mutants thus examined, 16 gave two types of segregants, glutamate requirers and non-requirers, in ratios from 200:3 to 3:50. Every attempt to find a constant segregation ratio ended in failure because of technical difficulties. In this connection, it must be noted here that the technique adopted for picking up conidia free from the back-ground cells was reliable and justified by reconstruction tests with auxotrophic and prototrophic strains. Anyhow, the fact that most of the colonies appearing on minimal medium were heterogenous with regard to conidial type suggests that the conidia forming them must have had two genetic units. The same conclusion was drawn from the reversion tests with other types of biochemical mutants.

For the reasons mentioned above, we wish to propose that the conidia studied here seem uninucleate but the nucleus is really bipartite or diploid.

H. SAITO and Y. IKEDA

Institute of Applied Microbiology, University of Tokyo (Japan), July 23, 1957.

Résumé

1° L'étude cytologique a montré que les conidia de *Streptomyces griseoflavus* sont uninucléaires et que dans un conidium la substance chromatique a deux sphères durant la période qui précède sa maturation. 2° L'inactivation par rayons-X des conidia donne des courbes du type « deux-coups (two-hit) ». 3° Dans le cas d'isolation des mutants biochimiques de conidia irradiés par rayons ultraviolets, on a trouvé une apparence de mutation retardée probablement à cause du délai de ségrégation. 4° Le conidium de mutant venant d'auxotrophe par réversion comprend des unités génétiques hétérogènes.

Ces quatre faits indiquent que les conidia de cette souche ont les nuclei bipartites ou diploides.

Biosynthesis of Benzylpenicillin by Mycelial Suspensions of *Penicillium chrysogenum*

The biosynthesis of benzylpenicillin by the mycelia of *Penicillium chrysogenum* involves the utilization of the immediate precursors L-cysteine, the non-nitrogenous moiety of valine, phenylacetic acid (PA), and an amino group donating compound (amino acid?)¹. The exact mechanism of synthesis and the enzyme systems involved require to be elucidated and work is in progress in this laboratory towards this end. In view of the observations of HALLIDAY and ARNSTEIN² and of DEMAIN³ published recently, we report our results on the biosynthesis of benzylpenicillin by the resting cells of *P. chrysogenum*.

We utilized the mycelia grown (in the fermentors used for manufacture) in corn steep-peanut meal-lactose medium with sodium phenylacetate added every 6–8 h. The mycelial suspension was withdrawn from the fermentor at the specified hours, a measured volume taken, the mycelia separated from the broth by squeezing with cloth and washed twice or thrice by resuspending in sterilised distilled water and squeezing with cloth (this consistently removed all the penicillin adhering to the mycelium). The washed mycelium was resuspended in 0.01 M phosphate buffer (pH 7.0) to make up to the

original volume of the broth, 100 ml of the mycelial suspension distributed into each of the 500 ml conical flasks and the compounds to be studied added to the individual flasks. These were shaken in a rotary shaker giving 250 r.p.m. in a room maintained at 24°C. Samples (5 ml) were taken at the required intervals and the penicillin content of the filtered solution determined by bioassay according to the method of HUMPHRY and LIGHTBOWN⁴.

Mycelia from different batches were used for the different sets of experiments and so to check the variations there was included in every trial a control flask with PA (0.05%) and lactose (1%). The washed mycelium suspended in buffer or lactose alone produced only negligible amounts of penicillin for a few hours. Tables I, II, and III give some of the results obtained indicating the relative effectiveness of the various carbohydrates added. Sucrose gives the best results of the sugars, and phenylacetamide seems to be better than PA.

Table I
39 h mycelium (batch 1270), washed, and resuspended in phosphate buffer (P. amide: Phenylacetamide)

Constituents added	Penicillin titre in units per ml after			
	4 h	8 h	12 h	16 h
PA (0.05%)	47	96	120	124
PA (0.05%) + Lactose (1%)	55	155	210	300
P.amide (0.05%)	67	136	—	—
P.amide (0.05%) + Lactose (1%)	78	240	300	353

The following results, not reported in the tables to save space, were also obtained: arabinose, xylose, sodium and ammonium acetates (the sodium salt giving better results than the ammonium salt), sodium lactate and pyruvate (the two free acids showing inhibition),

¹ H. R. V. ARNSTEIN and P. T. GRANT, *Biochem. J.* **57**, 353 (1954); **57**, 360 (1954). – H. R. V. ARNSTEIN and M. CLUBB, *Biochem. J.* **60**, XXXIV (1955). – C. M. STEVENS, P. VOHRA, E. INAMINE, and O. A. ROHOT, *J. biol. Chem.* **205**, 1001 (1953). – C. M. STEVENS, P. VOHRA, H.E. MOORE, and C. W. DE LONG, *J. biol. Chem.* **210**, 713 (1954). – C. M. STEVENS, P. VOHRA, and C. W. DE LONG, *J. biol. Chem.* **211**, 297 (1954). – C. M. STEVENS, E. INAMINE, and C. W. DE LONG, *J. biol. Chem.* **219**, 405 (1956). – O. K. SEBEK, *Proc. Soc. exper. Biol. and Med. N. Y.* **84**, 770 (1953). – M. GORDON, S. C. PAN, A. VIRGONA, and P. NUMEROF, *Science* **118**, 43 (1953). – E. MARTIN, J. BERKY, C. GODZESKY, P. MILLER, J. TOME, and R. W. STONE, *J. biol. Chem.* **203**, 239 (1953). – K. GANAPATHI, *Antibiotic Symposium (Pimpri)*, March 28 (1956) (in press); *Exper.* **13**, 172 (1957).
² W. J. HALLIDAY and H. R. V. ARNSTEIN, *Biochem. J.* **64**, 380 (1956).
³ A. L. DEMAIN, *Arch. Biochem. Biophys.* **64**, 74 (1956).

⁴ J. H. HUMPHRY and J. W. LIGHTBOWN, *J. gen. Microbiol.* **7**, 129 (1952).

Table II
36 h mycelium (batch 1240), washed, and resuspended in phosphate buffer

Constituents added	Penicillin titre in units per ml after					
	4 h	8 h	12 h	16 h	20 h	24 h
PA (0.05%) + Lactose (1%) . . .	10	35	65	156	227	348
PA (0.05%) + Sucrose (1%) . . .	34	100	188	242	321	370
PA (0.05%) + Glucose (1%) . . .	5	23	43	122	184	247
PA (0.05%) + Mannose (1%) . .	8	26	35	145	188	232
PA (0.05%) + Fructose (1%) . .	6	34	62	145	214	273

Table III
34 h mycelium (batch 1239), washed, and resuspended in phosphate buffer.

Constituents added	Penicillin titre in units per ml after					
	4 h	8 h	12 h	16 h	20 h	24 h
PA (0.05%) + Lactose (1%) . . .	16	45	106	216	280	296
PA (0.05%) + Fructose (1%) . .	20	65	117	232	233	221
PA (0.05%) + Starch (1%) . . .	14	50	90	77	0	0
PA (0.05%) + Dextrin (1%) . . .	17	28	120	184	225	315

arachis oil and oleic acid were found to increase the rate of synthesis of penicillin, though not as effectively as lactose. Sodium benzylpenicilloate, prepared from benzylpenicillin, was inefficient as the penicillin precursor. The seed mycelium (prepared in corn steep liquor-sucrose medium by inoculating with the spores and aerating for 48 h and used to inoculate the fermentors) did not produce any penicillin as such or with PA, lactose, L-cystine and L-valine. The penicillin-producing capacity of the mycelium in the fermentor varies with the age of the mycelium, rising to a peak at 36–45 h and then declining. The observation of HALLIDAY and ARNSTEIN² that crushing the mycelium destroys the penicillin producing capacity is confirmed.

The use of the washed mycelial suspensions as adopted in these experiments excludes the metabolites found in the fermented broth from participating in the biosynthesis, and satisfies the two conditions now taken to be essential for penicillin synthesis, viz. the mycelium should not be actively multiplying and the pH of the medium should be about 7.0⁵. The following picture of penicillin production by the mycelium emerges from the present studies. The mycelium prepared as seed to inoculate the big fermentors probably lacks the enzyme systems essential for penicillin synthesis. The mycelium in the production fermentors gradually builds up endogenously the enzyme systems essential for biosynthesis as well as for providing energy for the synthetic steps and also the substrates except PA. For continued penicillin production at a good rate, the mycelium requires PA from the exogenous source and also energy which seems to be provided by some saccharides, arachis oil, oleic acid, and acetate acting as substrates.

Fuller details of the work and discussion of the results will be published elsewhere.

We are indebted to Dr. P. D. KULKARNI, Miss I. NALINI, and Mr. D. N. BILAMPALLY for the bioassays reported here.

V. N. DESHPANDE and K. GANAPATHI

Antibiotics Research Centre, Hindustan Antibiotics (P) Ltd., Pimpri (Poona District, India), May 17, 1957.

Résumé

Les auteurs ont étudié les effets des divers hydrates de carbone (glucose, fructose, mannose, galactose, xylose, arabinose, lactose, amidon et dextrine), du pyruvate, du lactate, de l'acétate, de l'huile d'arachide, etc. sur la biosynthèse de la pénicilline par les cellules lavées de *P. chrysogenum*.

⁵ M. J. JOHNSON, Bull. World Health Org. 6, 99 (1952).

On the Role of Purines in the Enzymatic Reduction of Tetrazolium Salts

In the past, three prime functions of purines and their derivatives in the cellular economy have been elucidated, namely in the formation of nucleoproteins, in energy-conservation mechanism and in some transfer reactions of carbohydrates and phospholipides. That still other functions exist for this important group of compounds is attested to by the role of hypoxanthine in the oxida-

tion of sulphite¹, cysteine², and fatty acids³, and of adenosine-5'-monophosphate (AMP) in L-amino acid decarboxylation⁴. It has also been recently found⁵ that a wide variety of such compounds function in tetrazolium salt reduction. Thus, purine, hypoxanthine and related compounds⁶ can replace the heat-stable factor, found in various animal tissues and in yeast, which is necessary for the enzymatic reduction of tetrazolium salts⁷. The purpose of the present communication is to report the findings that this activation by purines and purine derivatives, although first detected by us in the case of an amine dehydrogenating system, is observed with quite diverse substrates when a tetrazolium salt is used as the terminal electron acceptor.

Methods.—Washed particles of homogenized rat liver or, alternatively, solubilized enzyme preparations⁸, were used as sources of enzyme. Reaction mixtures contained, in a final volume of 2.0 ml, 40 μ moles of phosphate buffer, pH 7.4; 20 μ moles of substrate; 4.8 μ moles of triphenyltetrazolium chloride or neotetrazolium chloride (expressed in monotetrazolium units); 0.4 μ mole of pyocyanine; 0.1–0.3 μ mole of cofactor (i.e. purine, etc.); and 28–35 mg (dry wt.) of dialyzed liver extract. Pyocyanine was added to aid the transfer of hydrogen from substrate to the tetrazolium⁹, but it was not an obligatory component. The solutions were incubated in a waterbath at 37° for 15–40 min at which time the cofactor was added. This preincubation of substrate and enzyme assured maximal rate of tetrazolium reduction. The appearance of formazan with amine substrates usually depended upon the addition of the cofactor, but occasionally a small amount was formed before supplementation. The reaction was followed by the increase in absorbance of the reaction mixtures at 520 m μ , read directly in the Coleman Junior Spectrophotometer. Under these conditions formazan production has been observed to proceed briskly for a short period, reaching a plateau in 5–15 min. This was the case when hypoxanthine, xanthine, purine, guanine, inosine and diphosphopyridine nucleotide (DPN) were used. At the plateau the molar ratio of 'formazan produced: cofactor added' varies between 0.5 and 1.5. Adenine, 6-methylpurine, azaguanine, uric acid and alloxan were inactive in this test system⁶.

Results.—Many substrates were tested as hydrogen donors with a tetrazolium salt as the ultimate acceptor (Table). Among the amines, tyramine and isoamylamine had an absolute requirement for this cofactor; with tryptamine and benzylamine the rate of reduction of the dye was markedly accelerated by the cofactor. Choline and succinate were also dehydrogenated in the unsupplemented reaction mixtures but addition of cofactor in-

¹ I. FRIDOVICH and P. HANDLER, J. biol. Chem. 221, 323 (1956).

² I. FRIDOVICH and P. HANDLER, Biochim. biophys. Acta 21, 173 (1956).

³ E. ANNAU, A. EPERJESSY, and O. FELSZEZGHY, Z. physiol. Chem. 277, 58 (1943). – K. BURTON, Nature 161, 606 (1948). – A. JACOB, C. R. Soc. Biol., Paris 147, 1044 (1953).

⁴ L. EGGLESTON, Biochem. J. 65, 735 (1957).

⁵ J. LAGNADO and T. L. SOURKES, Rev. Canad. Biol. 15, 258 (1956).

⁶ J. LAGNADO and T. L. SOURKES (in preparation).

⁷ J. LAGNADO and T. L. SOURKES, Can. J. Biochem. Physiol. 34, 1095 (1956).

⁸ G. COTZIAS, I. SERLIN, and J. GREENOUGH, Science 120, 144 (1954). – T. L. SOURKES and J. LAGNADO, J. Histochem. Cytochem. 5, 442 (1957).

⁹ D. GREEN, S. MILI, H. MAHLER, and R. BOCK, J. biol. Chem. 206, 1 (1954). – E. FARBER and C. LOUVIERE, J. Histochem. Cytochem. 4, 347 (1956).

creased the initial rate of formazan production. In the cases of isocitric and malic dehydrogenases, triphosphopyridine nucleotide¹⁰ was required in addition to a purine. It was not possible to demonstrate tetrazolium reduction with the following substrates, in the presence or absence of cofactor: glycine, serine, threonine, methionine, aspartic acid, spermine, histamine and 1,4-butanediamine.

The activating effects of inosine with various substrates

Substrate	Activity O.D. 520/10 min	
	No Inosine	Plus Inosine
Tyramine	0.000	0.920
Isoamylamine	0.000	0.860
Isocitrate	0.000	1.030
L-Malate	0.000	0.200
Benzylamine	0.175	0.830
Tryptamine	0.210	0.900
Choline	0.060	0.400
Succinate	0.150	0.790

In order to determine the specificity of the cofactor effect AMP, purine, hypoxanthine, adenine and uric acid were tested with several of the substrates. It was found that with succinate the first three compounds act in the same way as inosine (Table) and that adenine and uric acid are inactive, as they are with amines. It was also desirable to learn whether the cofactor which functions in tetrazolium reduction is also involved in the reduction of other dyes. Thus far it has not been possible to demonstrate this for methylene blue, 2,6-dichlorophenolindophenol or ferricyanide, although hypoxanthine is required in the specific case of sulphite/methylene blue¹.

Discussion.—Tetrazolium dyes are being used increasingly in enzymological and histochemical investigations, but in spite of this the kinetics and mechanism of their reduction are incompletely understood. BRODIE and GORS¹² have adduced evidence that tetrazolium salts accept protons from flavoproteins, but the present data indicate that the transfer system is probably more complex than this. The existence of a cofactor for tetrazolium reduction has been suspected previously. SPRINZ and WALDSCHMIDT-LEITZ¹³ detected requirement of a cofactor for succinic dehydrogenase when measured with tetrazolium. Diphosphopyridine nucleotide satisfied the requirement but, according to the authors, is probably not the natural factor. Others¹⁴ have made similar findings. The present results demonstrate, first of all, that certain purines, nucleosides and nucleotides, respectively, participate in the enzymatic reduction of tetrazolium salts; and, secondly, that this effect is specific for tetrazolium salts among the electron acceptors tested, i.e. it does not apply to the same enzyme preparations catalyzing the reduction of ferricyanide,

methylene blue, 2,6-dichlorophenol indophenol or oxygen. The nature and function of the cofactor is still somewhat speculative, but two possibilities can be envisaged: (1) The cofactor serves in proton transfer, serving at the pyocyanine or tetrazolium level. Because the molar ratio, monoformazan/purine, ranges between 0.5 and 1.5 it is evident that the cofactor does not behave like the usual catalytic agents. It is conceivable that immediately after transferring protons to the pyocyanine or tetrazolium the cofactor differs somewhat from the original compound, and it is unable to serve in the enzyme system, but that it is slowly reconverted to the original structure¹. This would account for molar ratios greater than unity, in that a portion of the cofactor would move through the entire cycle quickly enough to be utilized in the dehydrogenation more than once. (2) An alternative hypothesis is that the cofactor accepts the dehydrogenated substrate residue, resulting in a 'bound', inactive form of the cofactor. However, it is difficult to reconcile such a function with the variety of substrates and of purified compounds which are effective as cofactors.

From a comparison of the chemical structure of active substances it would appear that the 6 and 8 positions on the purine are of special importance. Thus, adenine and certain other 6-substituted analogues are inactive, as is azaguanine. The activity of adenosine and AMP may be explicable by their prior deamination, enzymes for which are found in the rat liver, although adenase is absent.

Acknowledgement.—Aided by a Dominion-Provincial Mental Health Grant and by a grant to Dr. R. A. CLEGHORN from the Foundations' Fund for Research in Psychiatry.

T. L. SOURKES and J. R. LAGNADO

Allan Memorial Institute of Psychiatry, McGill University, Montreal (Canada), September 2, 1957.

Zusammenfassung

Nach der vorliegenden Untersuchung können verschiedene Purine und einige ihnen nahestehende Verbindungen an der enzymatischen Reduktion der Tetrazole als Zwischenprodukte teilnehmen.

Oxygen Equilibrium of Human Myoglobins (Mb I and Mb II)¹

In previous research, we demonstrated that at least three components (Mb I, Mb II, Mb III) are present in the human muscle and in preparations of crystallized myoglobin (Mb). These components differ from one another in their electrophoretic behaviour².

In this note, we give the results of experiments aimed at studying the oxygen equilibrium of Mb I and Mb II. It has not been possible to make experiments with Mb III, because of the small quantities in which it is present in Mb solutions.

We have found these studies interesting to investigate the possible physiological meaning of these pigments,

¹⁰ This compound, unlike DPN, cannot serve as cofactor in the test system containing amine as substrate.

¹¹ E. SHELTON, in *Proceedings of the Histochemical Society*, J. Histochem. Cytochem. 4, 427 (1956).

¹² A. BRODIE and G. GOTS, *Science* 116, 588 (1951).

¹³ H. SPRINZ and E. WALDSCHMIDT-LEITZ, *Z. physiol. Chem.* 293, 16 (1953).

¹⁴ C. BARKER, *Fed. Proc.* 12, 9 (1953). — C. BRIL, *Biochim. biophys. Acta* 15, 258 (1954). — N. ZOLLNER and E. ROTHMUND, *Z. physiol. Chem.* 298, 97 (1954). — T. SUGIMURA and T. ONO, abstracted in *Chem. Abstr.* 50, 10142 (1956).

¹ Aided by a grant from the Rockefeller Foundation.

² A. ROSSI-FANELLI and E. ANTONINI, *Arch. Biochem. Biophys.* 65, 578 (1956).

and to establish, as seemed to be necessary in the course of a systematic research on the O_2 equilibrium of human Mb³, whether the dissociation curves of non-homogeneous crystallized Mb were different, and in which way, from those obtained with homogeneous preparations.

Preparation of crystallized human Mb.—Mb has been crystallized according to ROSSI-FANELLI⁴. The crystals were dissolved in H_2O and the solution obtained was dialyzed until the ammonium sulphate disappeared, and if necessary, the solution concentrated by freeze-drying.

Separation of the Mb components.—Components I and II were separated through preparative zone electrophoresis, using starch-gel supporting medium. The method used for the preparation of gel and for the elution of substances was basically that described by SMITHIES⁵.

Starch gels $23 \times 12 \times 1$ cm in size, in borate buffer pH 8.6, I 0.05 were used. The separation was obtained in 8 to 10 h, with a voltage gradient of 6–8 V/cm. It is possible to separate in each electrophoresis from 1 to 2 ml of a solution of Mb 1–3%. As can be seen by the experiment shown on Figure 1 (made in accordance with a technique described in a previous work²), the separated components are electrophoretically homogeneous.

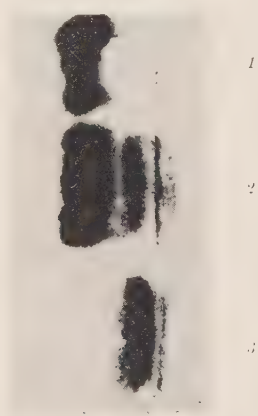


Fig. 1.—Paper electrophoresis of homogeneous Mb I (1), Mb II (3) and unhomogeneous crystallized myoglobin (2).

Determination of the O_2 dissociation curves.—The borate buffer solutions of the components I and II, obtained by elution from starch-gel, are brought from pH 8.6 to pH 8 with diluted acetic acid. Mb I is obtained in concentrations of 0.5–1%, and Mb II in 5 or 6 times weaker concentrations. The isolated components were reduced through the enzymatic system previously described⁶. The dissociation curves were determined by means of a spectrophotometric method which we have developed and which is particularly suited in the case of small quantities of pigment and of diluted solutions³.

Since Mb II can only be obtained in diluted solutions (0.5×10^{-4} M), we made a series of preliminary tests in order to ascertain the influence of the concentration of Mb on the O_2 dissociation curve. These experiments,

which were made either on non-homogeneous Mb or on Mb I, showed that the Mb concentration has no appreciable influence on the O_2 dissociation curve from 0.2 to 4.5×10^{-4} M. The dissociation curves of Mb I have therefore been determined using the same concentration of Mb as used in the case of Mb II.

The spectrophotometric readings were taken, with a light path of 2 mm, in the visible region ($\lambda = 510, 540, 560, 580$) and mainly for the diluted solutions, in the Soret zone ($\lambda = 415, 430$).

No difference was found between the oxygenation percentage, either when the readings were made in the visible region or in the Soret zone; and no appreciable difference between Mb I and Mb II in the extinction and maxima of the peaks of the oxygenated and deoxygenated derivatives.

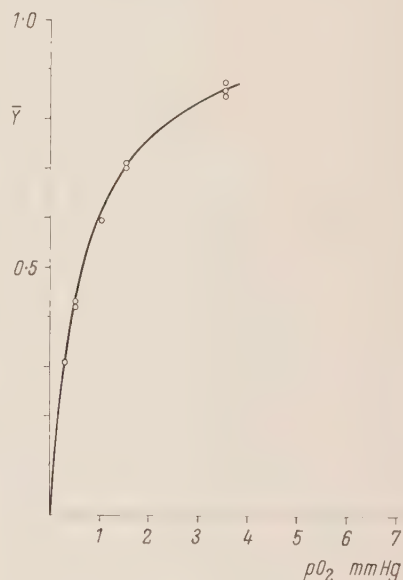


Fig. 2.—Oxygen dissociation curve of human Mb I (5×10^{-5} M) at 20° and pH 8; $p_{1/2} = 0.66$ mm Hg; $Y = MbO_2 / (MbO_2 + Mb)$.

Shape of the O_2 dissociation curve.—As shown in Figure 2 and 3, Mb I as well as Mb II have hyperbolic dissociation curves which follow the Hill equation:

$$MbO_2 / Mb = K (pO_2)^n \quad \text{with } n = 1.1^*$$

This result is very interesting, particularly as far as the minor component is concerned, because this property shows that it is a true myoglobin.

Oxygen affinity.—The experiments reported in Figure 2 and 3 show that at 20° and at pH 8 the two Mb have a very similar O_2 affinity. Actually, many dissociation curves for Mb II have given $p_{1/2}$ values slightly lower than those of Mb I and non-homogeneous Mb. These differences, however, are not far from the limit of the experimental error of the method.

Influence of temperature on oxygen affinity.—The influence of temperature on the O_2 dissociation curves of Mb I and Mb II was studied between 20° C and 40° C.

The Table and Figure 3 give the variation of the log K and $p_{1/2}$, with temperature, both for Mb I and Mb II.

It can be seen that the O_2 affinity at different temperatures is similar for both Mbs.

* MbO_2 and Mb denote concentrations.

³ A. ROSSI-FANELLI and E. ANTONINI (in press).

⁴ A. ROSSI-FANELLI, *Haemoglobin* (Butterworth's Sci. Publ., London 1949), p. 115.

⁵ O. SMITHIES, *Biochem. J.* **61**, 629 (1955).

⁶ A. ROSSI-FANELLI, E. ANTONINI, and B. MONDOVI, *Arch. Biochem. Biophys.* **68**, 341 (1947).

The overall heat of reaction calculated by the Van't-Hoff equation between 20° and 40° was found to be: for Mb I $\Delta H = -13.500$ cal., and for Mb II $\Delta H = -13.300$ cal.

The results we have obtained show that the dissociation curves for Mb I and Mb II are very similar. The figures given for the minor component (Mb II) are highly interesting. This pigment shows all the properties

t °C	log K		$p \frac{1}{2}$ (mm Hg)	
	Mb I	Mb II	Mb I	Mb II
20	+ 0.18	+ 0.19	0.66	0.65
25	+ 0.03	+ 0.04	0.93	0.91
30	- 0.13	- 0.11	1.35	1.29
35	- 0.28	- 0.23	1.91	1.70
40	- 0.47	- 0.42	2.95	2.63

Values of log K and $p \frac{1}{2}$ for human Mb I and Mb II at different temperatures. $K = \text{MbO}_2/\text{Mb} \cdot p\text{O}_2$; $p \frac{1}{2}$ = oxygen pressure (at 20° C) for 50% saturation.

of a myoglobin: reversible combination with oxygen, shape of the dissociation curve, and affinity for O_2 , so that we must definitely give up the thought that we are dealing with an impurity or an artefact.

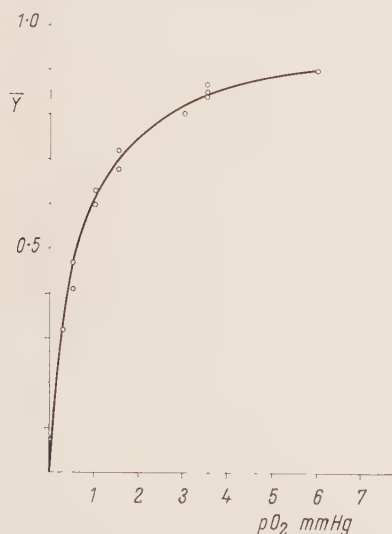


Fig. 3.—Oxygen dissociation curve of human Mb II (4×10^{-5} M) at 20° and pH 8; $p \frac{1}{2} = 0.65$ mm Hg; $Y = \text{MbO}_2/\text{Mb} + \text{MbO}_2$.

As far as the two Mb are concerned, and we have demonstrated their presence also in the muscle extract, we can state that they are perfectly equivalent in their most typical physiological property: that is, the reversible combination with O_2 . We must reject the hypothesis that Mb II is a residue of foetal Mb; experiments which we have carried out demonstrate that foetal Mb cannot be separated in electrophoresis from adult Mb, and that the preparations of foetal Mb show the presence of several components which have electrophoretic characteristics similar to those found in adult Mb.

The above results show that studies (also with spectrophotometric methods) on the equilibrium between human Mb and O_2 can be rightly based on non-homogeneous crystallized pigment particularly because Mb I and Mb II have identical absorption spectra.

Research on the structure of the pigment must, on the other hand, be based on homogeneous preparations. Results of the preliminary research which we have

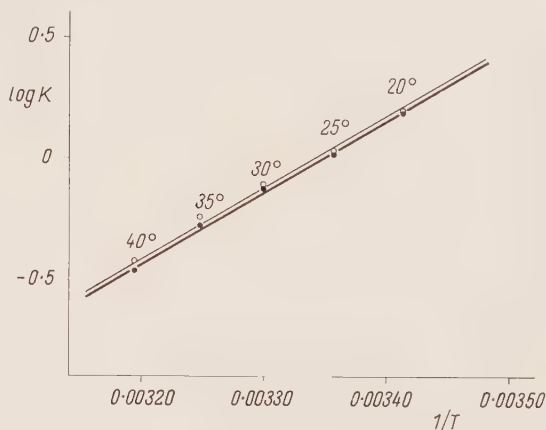


Fig. 4.—Influence of temperature on oxygen affinity of human Mb I = ● and Mb II = ○; pH 8, borate buffer I 0.05; $K = \text{MbO}_2/\text{Mb} \cdot p\text{O}_2$.

carried out lead us to think that the two Mb have different chemical natures, as seems to be the case with horse-Mb⁷.

Research along this line is in progress in our Institute.

A. ROSSI-FANELLI and E. ANTONINI

Institute of Biological Chemistry, University of Rome (Italy), August 5, 1957.

Riassunto

Dalla mioglobina umana cristallizzata sono stati isolati, a mezzo dell'elettroforesi su gel di amido, due componenti puri ed omogenei: Mb I e Mb II. Dei due componenti sono state determinate, in varie condizioni sperimentali, le curve di dissociazione per l'ossigeno.

⁷ H. T. THEORELL and A. AKESON, *Ann. Acad. Sci. fenn.* **60**, 303 (1955). — H. THEORELL, Personal Communication.

Über die Alkaloide von *Rauwolfia ligustrina* R. & S. Raugustin, ein neues reserpinähnliches Alkaloid*

Von den amerikanischen *Rauwolfia*-Arten sind bis heute ausser *R. sellowii* Muell.-Arg.², *R. grandiflora* Mart.³ und *R. schueli* Speg.⁴ hauptsächlich die nach der neuen Klassifikation von RAO⁵ unter der Bezeichnung

* 30. Mitteilung über *Rauwolfia*-Alkaloide¹.

¹ 29. Mitteilung siehe C. F. HUEBNER und E. SCHLITTLER, *J. Amer. chem. Soc.* **79**, 250 (1957).

² F. A. HOCHSTEIN, *J. Amer. chem. Soc.* **77**, 5744 (1955). — S. C. PAKRASHI, C. DJERASSI, R. WASICKY und N. NEUSS, *J. Amer. chem. Soc.* **77**, 6687 (1955).

³ W. B. MORS und P. ZALTZMAN, *Chem. and Ind.* **1956**, 173.

⁴ G. IACOBucci und V. DEULOFEU, *J. org. Chem.* **22**, 94 (1957).

⁵ A. S. RAO, *A Revision of Rauwolfia with Particular Reference to the American Species* (Diss.), *Annals of the Missouri Botanical Garden* **43**, 253 (1956).

R. tetraphylla L.⁶ zusammengefassten Varietäten chemisch untersucht worden⁷. Über *R. indecora* Woodson⁸ und *R. ternifolia* H.B.K.⁹, welche nach RAO¹⁰ zusammen mit *R. alphoniana* Muell.-Arg. und *R. parvifolia* Bert. ex Spreng. und ihren Varietäten heute als *R. ligustrina* R. & S. bezeichnet werden müssen, sind nur unvollständige Angaben bekannt. Erst in jüngster Zeit haben diese durch die papierchromatographischen Untersuchungen von KORZUN *et al.*¹¹ eine gewisse Erweiterung erfahren.

Wie die nahe verwandte *R. tetraphylla*, so besitzt auch *R. ligustrina* ein unerwartet reichhaltiges Alkaloidspektrum¹². Neben Reserpin haben wir durch fraktionierte Extraktion, Chromatographie und Gegenstromverteilung die bereits bekannten Alkaloide Tetrahydroalstonin, Aricin, Ajmalicin, Isoreserpin, Isoreserpinin, Reserpin, Deserpidin, Pseudoreserpin, α -Yohimbin, Ajmalin, Sarpagin, Serpentinin, Serpentin und ein bisher unbekanntes Alkaloid, das wir *Raugustin* nennen, isoliert. Papierchromatographisch liessen sich ausserdem in geringen Mengen Rescinnamin, Isoreserpin, Renoxydin¹³, Raunescin, Isoraunescin, Yohimbin und einige seiner Isomeren, sowie noch vier bisher nicht identifizierte Basen nachweisen¹⁴. Die Ausbeute an kristallisiertem Reserpin beträgt nach sorgfältigem Chromatographieren der Mutterlaugen 0,085%. Mit einem Gehalt von etwa 1% des Gewichtes der luftgetrockneten Wurzeln stellt Reserpin das Hauptalkaloid dar.

Die Isolierung des neuen Alkaloides Raugustin neben der schon bekannten Base Pseudoreserpin¹⁵ und der nachgewiesene Gehalt an Raunescin und Isoraunescin¹⁶ lenkten unsere Aufmerksamkeit auf die Gruppe der an den Hydroxylfunktionen unvollständig methylierten reserpinähnlichen Basen. Wie HOSANSKY und SMITH¹⁷ vermutet und HUEBNER und SCHLITTLER¹ bewiesen haben, bilden Raunescin (I) und Isoraunescin (II) ein Paar von Isomeren, welche je eine freie Hydroxylgruppe

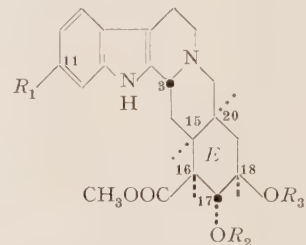
im Ring E enthalten und sich einzig durch verschiedene Verknüpfungsstellen der esterartig gebundenen 3,4,5-Trimethoxybenzoesäure unterscheiden. Ihr Ringgerüst entspricht in seinem sterischen Bau demjenigen des Deserpidins⁷ (III).

Tabelle I

	R ₁	R ₂	R ₃
Raunescin (I)	H	H	Tmb
Isoraunescin (II)	H	Tmb	H
Deserpidin (III)	H	CH ₃	Tmb
Pseudoreserpin (IV)	OCH ₃	H	Tmb
Raugustin (V)	OCH ₃	Tmb	H
Reserpin (VI)	OCH ₃	CH ₃	Tmb

Tmb = 3,4,5-Trimethoxybenzoyl-Rest

Auf Grund der nachfolgenden Daten nehmen wir eine analoge Strukturbeziehung für die drei am Kohlenstoffatom 11 methoxylierten Basen Pseudoreserpin (IV), Raugustin¹⁸ (V) und Reserpin (VI) an.



Raugustin befindet sich wie die andern Alkaloide der Reserpingruppe in der Fraktion der schwachen Basen und wird durch Chromatographie an Aluminiumoxyd und Reinigung über das schwerlösliche Nitrat gewonnen. Auf Grund der Analysenwerte für die Base und das Nitrat (Tabelle II) ergibt sich die Bruttoformel $C_{32}H_{38}O_9N_2 \cdot (H_2O)$ für Raugustin. Es besitzt 5 O-Methyl-, keine N-Methyl- und keine C-Methyl-Gruppen, ferner 2 aktive Wasserstoffatome (NH, OH). Die optische Drehung, $[\alpha]_D^{24}$ beträgt $-50^\circ (\pm 4^\circ)$, ($c = 0,609$ in Chloroform).

Das Ultraviolett-Absorptionsspektrum in Alkohol zeigt die beim Reserpin und Pseudoreserpin beobachteten Maxima bei $217 m\mu$ ($\epsilon = 54600$) und $268 m\mu$ ($\epsilon = 15400$), die Schulter bei $291 m\mu$ ($\epsilon = 9300 m\mu$) und ein ausgeprägtes Minimum bei $246 m\mu$ ($\epsilon = 9000$), welche für das gleichzeitige Vorhandensein einer 6-Methoxyindol-Gruppierung und eines 3,4,5-Trimethoxybenzoyl-Restes charakteristisch sind¹⁹.

Wie beim Isomerenpaar Raunescin und Isoraunescin, so besteht auch für Pseudoreserpin und Raugustin eine weitgehende Übereinstimmung der Infrarot-Spektren. Ausser einer schwachen Absorptionsbande bei $2,77 \mu$, welche einer freien Hydroxylgruppe zugeschrieben wird,

¹⁸ Die Bezeichnung «Iso-pseudoreserpin», welche in Analogie zu «Iso-raunescin» ursprünglich vorgesehen war, lässt sich heute nicht mehr verwenden, weil in der neueren Alkaloidforschung die Silbe «Iso-» für die am Kohlenstoffatom 3 epimere Verbindungsreihe gebräuchlich ist und von M. W. KLOHS *et al.* in diesem Sinne auch schon benützt worden ist. Korrekterweise müsste auch der Name Isoraunescin abgeändert werden.

¹⁹ L. DORFMAN *et al.*, Helv. chim. Acta 37, 59 (1954).

⁶ A. S. RAO, Annals of the Missouri Botanical Garden 43, 285 (1956): Mit *R. tetraphylla* L. sind unter anderem synonym *R. hirsuta* Jacq., *R. canescens* L., *R. heterophylla* R. & S., *R. tomentosa* Jacq. usw.

⁷ Eine Zusammenstellung der diesbezüglichen Literatur befindet sich zum Beispiel bei *Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology* by R. E. WOODSON, Jr., H. W. YOUNGKEN, E. SCHLITTLER und J. A. SCHNEIDER (Verlag Little, Brown & Company, Boston, Toronto, 1957).

⁸ M. ISHIDE, M. OKADA und K. SAITO, Pharm. Bull. (Japan) 3, 320 (1955).

⁹ H. T. CARDOSO und I. A. A. VENANCIO, Rev. bras. Biol. 16 (2), 231 (1956).

¹⁰ A. S. RAO, A Revision of *Rauwolfia* with Particular Reference to the American Species (Diss.), Annals of the Missouri Botanical Garden 43, 299 (1956).

¹¹ B. P. KORZUN, A. F. ST. ANDRÉ und P. R. ULSHAFFER, J. Amer. pharm. Ass. (im Druck).

¹² Das Material wurde in verdankenswerter Weise von Prof. A. DUCKE, Fortaleza und Dr. D. DE ANDRADE LIMA, Recife, Brasilien, gesammelt und identifiziert.

¹³ P. R. ULSHAFFER, W. I. TAYLOR und R. H. NUGENT, C. R. Acad. Sci., Paris 244, 2989 (1957), Renoxydin = Reserpin-N-oxyd.

¹⁴ Über Einzelheiten der Auftrennung des Alkaloidgemisches und die papierchromatographische Arbeitsmethode wird später berichtet.

¹⁵ M. W. KLOHS, F. KELLER, R. E. WILLIAMS und G. W. KUSSEROW, Chem. and Ind. 1956, 187; J. Amer. chem. Soc. 79, 3763 (1957).

¹⁶ N. HOSANSKY und E. SMITH, J. Amer. pharm. Ass. 44, 639 (1955). – C. F. HUEBNER und E. SCHLITTLER, J. Amer. chem. Soc. 79, 250 (1957). – Vgl. auch: E. E. VAN TAMELEN und C. W. TAYLOR, J. Amer. chem. Soc. 79, 5256 (1957). (Anmerkung bei der Korrektur.)

¹⁷ N. HOSANSKY und E. SMITH, J. Amer. pharm. Ass. 44, 639 (1955).

Tabelle II

	Schmelzpunkte (alle korrigiert)		Elementaranalyse		
			C %	H %	N %
Raugustin-Hydrat C ₃₂ H ₃₈ O ₈ N ₂ · H ₂ O	160–170° (Zers.) (im Vakuumröhrchen)	Ber. Gef.	62,73 62,52	6,58 6,87	4,57 4,51
Raugustin-Nitrat C ₃₂ H ₃₈ O ₉ N ₂ · HNO ₃	262–263° (Zers.) (im Vakuumröhrchen)	Ber. Gef.	58,44 58,68	5,98 6,08	6,39 6,38
Monoacetyl-Raugustin C ₃₄ H ₄₀ O ₁₀ N ₂	232–234° (Zers.) (Kofler-Block)	Ber. Gef.	64,14 63,93	6,33 6,22	4,40 4,34
			1 Acetyl: Ber. 2,36; Gef. 2,55%.		

deckt sich das IR-Spektrum des neuen Alkaloides im kürzerwelligen Teil vollständig mit demjenigen des Reserpins. Chemisch lässt sich diese Hydroxylgruppe durch die Bildung eines O-Acetylderivates (vgl. Tabelle II) mit Acetanhydrid in Pyridin nachweisen.

Einen konfigurativen Hinweis vermittelt das IR-Spektrum durch die Gestalt der Absorptionsbande bei 3,4 μ , welche auf ihrer längerwelligen Seite eine schwach ausgebildete Schulter aufweist. Sie deutet darauf hin, dass das Kohlenstoffatom 3 entsprechend der von WENKERT und ROYCHAUDHURI²⁰ beobachteten Gesetzmässigkeit die β -Konfiguration besitzt.

Gewisse physikalisch-chemische und biologische Eigenschaften des Raugustins erhärten seine strukturelle Verwandtschaft mit dem Isoraunescin. So verhalten sich, zum Beispiel, beide Basen praktisch gleichartig gegenüber Zweiphasen-Verteilungssystemen und bei der Papierchromatographie. Andererseits haben pharmakologische Versuche gezeigt, dass Raugustin²¹ wie Isoraunescin¹ nicht reserpinähnlich wirkt, insbesondere keine sedativ-hypnotische Wirkung besitzt. Beide Tatsachen legen nahe, dass auch bei unserem neuen Alkaloid die Verknüpfungsstelle des 3,4,5-Trimethoxybenzoyl-Restes nicht derjenigen der biologisch wirksamen Verbindungen I, III, IV und VI entspricht und dieser sich wohl in Stellung 17 befindet.

Alle bis heute bekannten Eigenschaften stützen die für Raugustin vorgeschlagene Strukturformel V, wenn auch für die Konfiguration der Asymmetriezentren C 15, 16, 17, 18 und 20 noch keine hinreichenden Beweise bestehen. Zur Abklärung dieser Frage haben wir versucht, unser Alkaloid in ein mit Pseudoreserpin gemeinsames Abbauprodukt überzuführen. Da letztere Verbindung das Ringgerüst des Reserpins besitzt²², wäre bei Identität der Reaktionsprodukte die Konstitution des Raugustins ebenfalls bewiesen.

Für die Methanolyse der beiden Alkaloide stand jedoch nur sehr wenig Material zur Verfügung, und es gelang jeweils nur, die 3,4,5-Trimethoxybenzoesäure, nicht aber das Methylpseudoreserpat in kristallisierter Form zu isolieren. Sobald mehr Ausgangsmaterial vorhanden ist, soll dieser Identitätsnachweis durch direkten Vergleich der stickstoffhaltigen Komponenten noch erbracht werden.

J. M. MÜLLER

Forschungslaboratorien der CIBA Aktiengesellschaft,
Pharmazeutische Abteilung, Basel, 24. September 1957.

²⁰ E. WENKERT und D. K. ROYCHAUDHURI, J. Amer. chem. Soc. 78, 6417 (1956).

²¹ Die pharmakologischen Prüfungen wurden in der Biologischen Abteilung der CIBA AG durchgeführt und seien Herrn PD Dr. H. J. BEIN bestens verdankt.

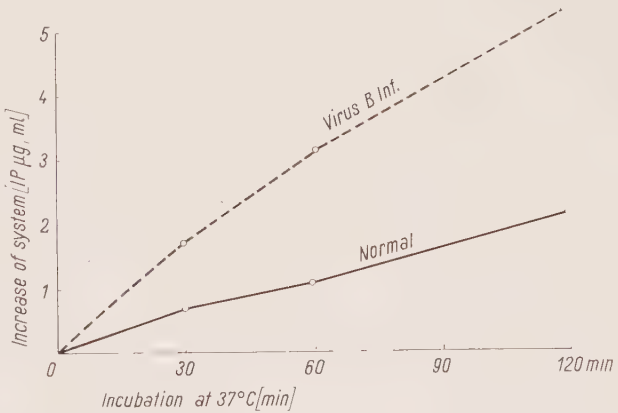
²² M. W. KLOHS, F. KELLER, R. E. WILLIAMS und G. W. KUSSEROW, J. Amer. chem. Soc. 79, 3763 (1957).

Summary

Twenty-one alkaloids have been identified from the root of *Rauwolfia ligustrina* R. & S. The more important ones are reserpine, pseudoreserpine and raugustine, a new base which is isomer to pseudoreserpine. The structure of the latter compound is discussed.

The Effect of Virus B on Enzyme-Systems
of the Host, *in vivo* and *in vitro*¹

Virus B was first isolated and thoroughly studied by SABIN². For the present study rabbits were infected intracerebrally or intramuscularly with 0.2 ml of 1/100 diluted infected tissue culture (TC) fluid. The animals were killed after exhibiting typical symptoms of the disease³. Fluids of Maitland-type of cultures, suspect for harboring virus B, were inoculated into TC of Rhesus kidney cortex and incubated for 6 days at 37°C; repeated subcultures helped to reach the final diagnosis. Supernatant of centrifuged brain homogenates (2000 r.p.m. for 10 min) of 4 animals and roller tube TC (6 batches) were assayed⁴. Standard techniques served for enzyme determinations⁵. Table I shows typical results. The decrease of common phosphomonoesterases and DNA-ases was in contrast with the great increase of RNA-ases and 5-nucleotidases (5-NT-ase, Figure).



¹ This work was supported by a Public Health Grant of the Ontario Department of Health, Canada.

² A. M. SABIN, Brit. J. exp. Path. 25, 321 (1934). – A. B. SABIN and A. M. WRIGHT, J. exp. Med. 59, 115 (1934).

³ A. M. SABIN, Brit. J. exp. Path. 25, 321 (1934).

⁴ Courtesy of Dr. D. L. McLEOD and Dr. G. H. MACMORINE, Connaught Medical Research Laboratories, University of Toronto.

⁵ E. KOVACS, Proc. Soc. exp. Biol. Med. 92, 183 (1956).

Table I
Effect of Virus B in Phosphomonoesterases and Nucleases of Brain

Extract of fresh frozen rabbit brain in water	Phosphatases ¹		Simple ¹ nucleotid- ase	RNA-ases ² acid alkaline		DNA-ases ³ acid alkaline		Turbidity Klett units/ml of system
	acid	alkaline						
	pH 5	pH 10.9		pH 5	pH 7.6	pH 5	pH 7	
Normal supernatant of 10% 'Brei' mean of duplicate assays.	5.6	2.4	1.0	11.3	0.0	12.2	6.4	1950
Infected intracerebrally inocula- tion with virus B.	4.1	1.7	0.5	34.0	2.0	6.4	3.0	1700

¹ Activity, as increase in IP μ g/ml of system; incubation 4 h at 37°C. Composition: 0.2 ml extract + 1.8 ml water + 6 ml buffered substrate (5.7).
² Activity, as increase in TASP μ g/ml of system; incubation 4 h at 37°C. Composition: 0.2 ml homogenate + 1.8 ml water + 2 ml of 0.5% RNA in buffer (5.7).
³ Activity, as % decrease of viscosity of system; incubation 2 h at 37°C. Composition: 0.2 ml + 2 ml buffer + 2 ml 0.5% DNA in water (5).

The tissue mass was also reduced in the infected brains as revealed by turbidimetry⁶. Results of assays on TC are shown in Table II. The decrease of phosphomonoesterases was noted simultaneously with the marked increase of both RNA-ases. The agreement between *in vitro* and *in vivo* findings is of special interest and means that some enzyme-changes are independent from inflammatory reactions. Additional aspects were investigated. For instance 8% increase in the activity of 5-NT-ase of infected 'brei' was found upon addition of 0.5 ml γ -globulin (commercial brand of Connaught M. R. Lab.). Similar amount had no effect on normal specimen. The 5-NT-ase activity of Russel's Viper venom (Haffkin Institute, Bombay) was significantly reduced (12%) when incubated for 30 min at 37°C, with normal and slightly with infected homogenate. The inhibition of

The decrease of common phosphomonoesterases and DNA-ase of brain extracts of virus B infected animals at the terminal stage of the disease, are in striking contrast with highly increased 5-NT-ase and RNA-ase activities. These latter are regarded as specific and fairly resistant biocatalysts, but there is much suggestion for a change in their kinetics or real increase in their concentration⁷. The changes may be causally connected with the cytopathogenic process⁸, but the time sequence and exact correlation has to be clarified. The agreements and discrepancies of experiments in animals and in TC cannot be explained at the present time. The similarity of increase of 5-NT-ase activity in some TC⁹, and in animals infected with MM virus¹⁰ may be an additional evidence for the primary nature of the enzyme-changes.

E. KOVACS* and J. KOVACS

Department of Public Health, School of Hygiene, University of Toronto, July 5, 1957.

Zusammenfassung

Im Hirnbrei von mit Virus B infizierten Kaninchen und in Gewebezuchten von Affennieren-Epithelien werden Veränderungen des Fermentgehaltes beobachtet. In beiden Fällen zeigt sich eine starke Zunahme der RNA-ase, während sich Nucleotidase, DNA-asen und Phosphomonoesterasen *in vivo* und *in vitro* nicht gleich verhalten.

⁷ E. KOVACS, J. exp. Med. 104, 356 (1956); Minerva Medica 48, 2157 (1957); G. Malatt. infett. parasit. (in press).
⁸ A. M. SABIN, Brit. J. exp. Path. 25, 321 (1934). – A. B. SABIN and A. M. WRIGHT, J. exp. Med. 59, 115 (1934). – E. KOVACS, Proc. Soc. exp. Biol. Med. 92, 183 (1956); J. exp. Med. 104, 356 (1956).
⁹ E. KOVACS, Minerva Medica 48, 2157 (1957); Biochem. Z. (in press).
¹⁰ E. KOVACS, Naturwissenschaften 44, 520 (1957).
* Present address: Hamburg, Stiftung zur Erforschung der spinalen Kinderlähmung und der multiplen Sklerose.

Table II
Effect of Virus B on Cultivated Rhesus Kidney Cells

TC in medium 597	5-nucleotidases	RNA-ases	
	pH 8.5	pH 5	pH 7.6
Normal monkey epithelium 14 days old cultures. Pool of 5 original tubes*	3.23	2.3	0.60
Similar cultures infected with Virus B. 6 days incu- bation	1.75	10.1	15.70

* Incubation for tests, 2 h at 37°C; for technique E. KOVACS, J. exp. Med. 104, 356 (1956); Minerva Medica 48, 2157 (1957); G. Malatt. infett. parasit. (in press).

5-NT-ase by polyvalent antivenom is of greater order in the infected (17 to 19%), than in the controls (5 to 10%). These not tabulated observations mean that some specific substance is missing in the latter, as suggested also by the different turbidity values and illustrate the altered biochemical behaviour of virusinfected tissues⁶.

⁶ E. KOVACS, J. exp. Med. 104, 356 (1956). – D. F. BAUER in: The Nature of Virus Multiplication, II. Symp. Soc. General microbiol. (Cambridge University press, 1953).

The Growth of Cartilaginous Embryonic Chick Bones After Freezing

I. *Introduction*.—Although considerable progress has been made in the development of techniques for freezing cells and tissues, attempts to preserve adult human cartilage at temperatures below 0°C have failed¹. Since cartilage undergoes considerable modification in its structure and metabolism during maturation the effect of freezing on embryonic cartilage is of interest, and in this paper the results of preliminary work on the freezing of cartilaginous tibiae from 6–7 day old chick embryos is described. These cartilaginous rudiments grow and differentiate in tissue culture², and therefore their response *in vitro* provides a very convenient test of viability after thawing.

II. *Material and Methods*.—The tibiae from 6 and 7 day old chick embryos were used in this work. The bones contained in small test tubes were cooled to -79°C in about 40 min using the freezing technique described by SMITH³. After the requisite period at -79°C had elapsed the bones were rapidly thawed by immersion of the tubes in a water bath at 37°C . The

bones were then removed, rinsed in Tyrode solution and transferred to the surface of the clotted plasma in the culture dishes.

The explants were cultivated at 37°C using the watch glass method for solid media⁴, some bones being kept for 3 days and others for 6 days. If the test lasted more than 3 days the medium was renewed. The medium consisted of 0.01 ml of 6.5% glucose solution, 0.375 ml fowl plasma and 0.125 ml of an extract in Tyrode of a minced chick embryo. The extract was prepared from a 13 day embryo in the first experiment and from a 9 day embryo in the second.

Two treatments were used in each experiment and these were allotted at random to one or other of the two tibiae from each embryo. Drawings were made with a camera lucida of the bones initially and again on the first and sixth days of cultivation. From these the length and maximum width of each epiphysis were determined. The average epiphyseal width of each bone is defined as the mean of the two maximum epiphyseal widths. The statistical analyses follow standard procedures and have been made after transformation of the data to the logarithmic scale.

III. *Results*.—(1) The tibiae from five chick embryos (7 days' incubation) were used in this experiment. The two treatments compared were (a) storage at -79°C for 1.5 h after freezing in 15% glycerol saline, and subsequent culture, and (b) culture without freezing (control treatment).

⁴ H. B. FELL and R. ROBISON, *Biochem. J.* 23, 767 (1929).

¹ R. C. CURRAN and T. GIBSON, *Proc. roy. Soc. [B]* 144, 572 (1956).

² H. B. FELL, *Skeletal development in tissue culture in The biochemistry and physiology of bone* (Ed. G. H. Bourne, Academic Press, New York 1956).

³ A. U. SMITH, *Exp. Cell Res.* 3, 574 (1952).

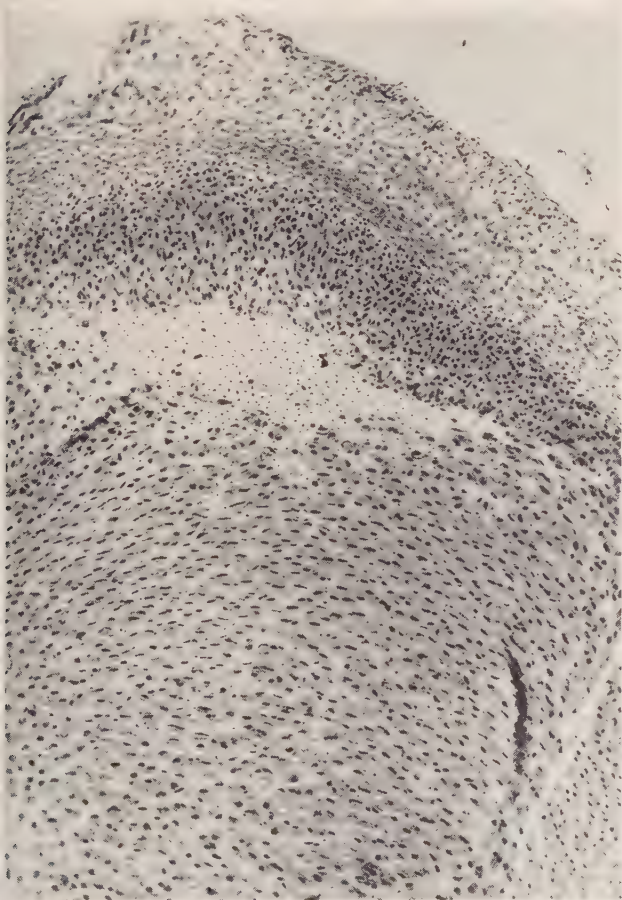


Fig. 1.—Epiphysis of a tibia cultivated for 3 days after freezing. $\times 126$.

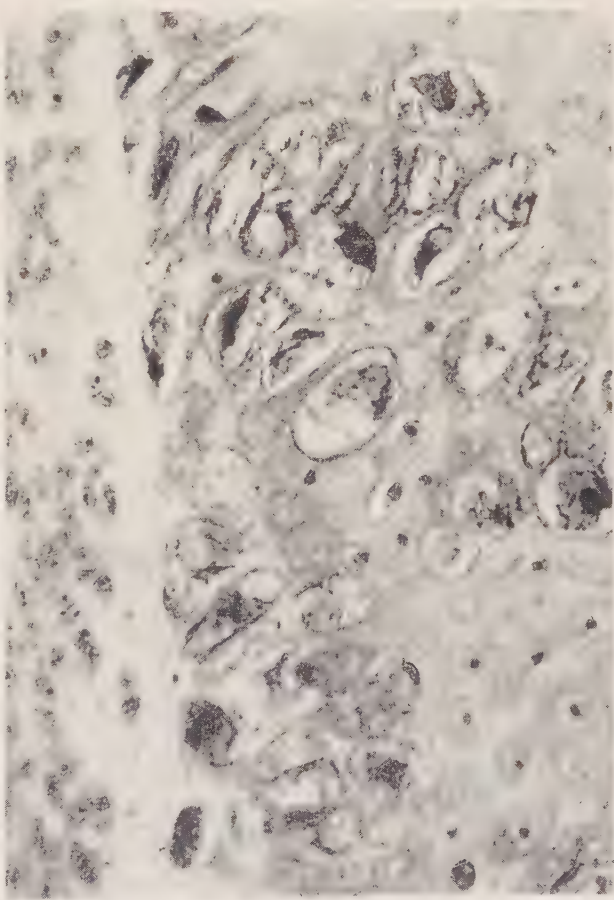


Fig. 2.—Diaphysis of a tibia cultivated for 3 days after freezing. 500.

The effect of freezing on the length and average epiphyseal width of 7 day old embryonic chick tibiae after 3 days' cultivation.

Treatment	Mean log length		Difference (d)
	Initial	Final	
Unfrozen . .	0.616	0.800	0.184
Frozen . . .	0.622	0.676	0.054

Standard error of d : 0.015, 8 D.F.

Treatment	Mean log epiphyseal width		Difference (d)
	Initial	Final	
Unfrozen . .	0.124	0.200	0.076
Frozen . . .	0.122	0.206	0.084

Standard error of d : 0.012, 8 D.F.

The measurements obtained from the camera lucida drawings made after 3 days' cultivation are summarized in the Table. The results demonstrate that although the frozen bones elongated to a significant degree ($t_{(8)} = 3.60$, $0.01 > P > 0.001$), the extent of the elongation was much less than that observed on the unfrozen controls. The Table also shows that considerable and equal growth of the epiphyses occurred in both the frozen and unfrozen bones.

Histological examination of the explants showed that the majority of the rounded epiphyseal and flattened cells survived the freezing, although in most specimens some cells in the centre of the epiphysis were dead (Fig. 1). In contrast, however, a large number of the cells in the diaphysis were dead. A few were alive and hypertrophied, but they appeared very distorted (Fig. 2). The periosteum and the zone of periosteal ossification was normal. In some specimens, cultivated for 6 days after freezing, mitotic figures were found in the outgrowth of fibroblasts, the periosteum and among the chondrocytes of the epiphysis.

(2) The tibiae from six chick embryos (6 days' incubation) were employed. The two treatments were storage for 1 h at -79°C and subsequent culture after (a) freezing in normal saline, and (b) freezing in 15% glycerol saline.

After 3 days' cultivation all the bones frozen in normal saline were dead. All the bones frozen in glycerol saline, however, survived the freezing. The degree of elongation varied from specimen to specimen. Two of the bones doubled their length and remained normal in shape, while the others elongated to a lesser degree accompanied by some distortion. In all specimens the epiphyseal and flattened cells were normal in appearance and showed mitotic activity. No necrosis was seen in these regions. Only a few cells were dead in the diaphysis, the majority being hypertrophic. In some regions of the diaphysis, however, the matrix was abnormal in structure, although it stained metachromatically with toluidine blue.

IV. *Discussion.*—The results show that it is possible to freeze, and subsequently revive, all parts of the cartilaginous tibiae from 6 day old chick embryos, provided glycerol is present in the freezing medium. In contrast, only the epiphysis of the tibiae from 7 day old embryos survive to any extent. Thus, during a period of 24 h normal growth and differentiation the majority of the cells in the diaphysis become sensitive to the effects of

freezing and are not protected by glycerol. At this stage of embryonic development the tibia undergoes rapid differentiation, the most spectacular change being the hypertrophy of the diaphyseal cells.

The causes of cellular damage on freezing, and the mechanism of the protective action of glycerol which is found with almost all tissues studied, has been analysed from a general point of view by LOVELOCK⁵. It is conceivable that the failure of glycerol to protect the diaphyseal cells is due to increased susceptibility to raised electrolyte concentrations or to the high glycerol concentrations. Changes in the permeability of the cell membranes may also be involved. Alternatively, the formation of matrix may retard the penetration of glycerol.

The results of freezing tibiae from 7 day old embryos is also of interest from a morphogenetic point of view, for the effect is to destroy differentially the zone of hypertrophic diaphyseal cells. In this zone, unlike the zones of epiphyseal and flattened cells, mitoses are rarely seen⁶. Thus, the fact that elongation of the bone is suppressed when the hypertrophic zone is destroyed demonstrates experimentally that the process of hypertrophy plays an important role in determining the shape of the developing cartilaginous rudiment.

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Department of Physiology, Royal Veterinary College, London, August 5, 1957.

Zusammenfassung

Tibien von sechs Tage alten Hühnerembryonen überleben eine Abkühlung auf -79°C . Im Gegensatz dazu werden die hypertrophischen Zellen der Diaphyse von Tibien siebentägiger Embryonen durch Gefrieren weitgehend zerstört, während der Rest der Rudimente überlebt.

⁵ J. E. LOVELOCK, *Biophysical aspects of the freezing of living cells in Preservation and transplantation of normal tissues* (Ed. G. E. W. Wolstenholme & M. P. Cameron; Churchill, London 1954).

⁶ H. B. FELL, *J. Morph.* **40**, 417 (1925).

Uracil Metabolism in *Neurospora crassa*

That a reductive pathway for pyrimidine catabolism exists was first suggested by FINK *et al.*¹. Later, by tracer experiments *in vitro* and *in vivo*², by chromatography³, and by enzyme studies⁴, it was established beyond doubt that thymine or uracil may be degraded to β -amino acids via the corresponding dihydropyrimidines and β -ureido acids in animal tissues.

¹ K. FINK, R. B. HENDERSON, and R. M. FINK, *J. biol. Chem.* **197**, 441 (1952).

² K. FINK, R. E. CLINE, R. B. HENDERSON, and R. M. FINK, *J. biol. Chem.* **221**, 425 (1956). — E. S. CANELLAKIS, *J. biol. Chem.* **221**, 315 (1956). — P. FRITZSON and K. F. NAKKEN, *Acta chem. scand.* **10**, 161 (1956). — P. FRITZSON, *J. biol. Chem.* **226**, 223 (1957). — P. FRITZSON and A. PIHL, *J. biol. Chem.* **226**, 229 (1957).

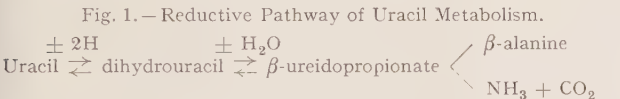
³ R. M. FINK, K. FINK, and R. B. HENDERSON, *J. biol. Chem.* **201**, 349 (1953). — R. M. FINK, C. MCGAUGHEY, R. E. CLINE, and K. FINK, *J. biol. Chem.* **218**, 1 (1956). — K. FINK, *J. biol. Chem.* **218**, 9 (1956).

⁴ S. GRISOLIA and D. P. WALLACH, *Biochim. biophys. Acta* **18**, 449 (1955). — D. P. WALLACH and S. GRISOLIA, *J. biol. Chem.* **226**, 277 (1957).

DiCARLO *et al.*⁵ first suggested that such a metabolic pattern is operative in microorganisms. Others⁶ have presented evidence that the reductive pathway of uracil is essentially the same in bacteria as in animal tissue. Apparently, there is a delicately balanced system between the degradation of uracil and its utilization for nucleotides⁷. The reductive pathway for uracil degradation is shown in Figure 1.

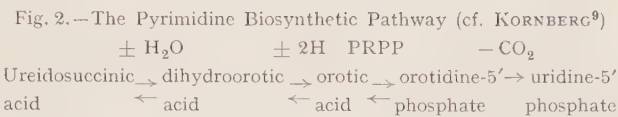
MITCHELL *et al.*⁸ reported on the properties of four distinct mutants of *Neurospora* that require pyrimidines for growth. This paper extends the observations of one of these mutants, Pyr-1 (263), to new substrates. The new substrates were suggested by the work of KORNBERG⁹, in which he has shown that pyrimidines are synthesized according to the pathway shown in Figure 2. The growth properties of Pyr-1, and other pyrimidine mutants which will be described elsewhere, are compatible with this scheme. This paper also describes the compounds accumulated by Pyr-1, and by wild-type 73a. These data are presented as evidence that a reductive pathway for uracil degradation, similar to the one reported for other organisms, exists in *Neurospora*, and that this pathway may be reversed to support growth of the pyrimidine-requiring mutant, Pyr-1.

The minimal medium used in these experiments is described elsewhere¹⁰. The pyrimidine supplements are added on a micro-molar equivalent (*mM* eq.) basis. (The molecular weight of uracil, 100 rather than 112, serves as a base.) The growth measurements reported are made from dried (24 h at 60°C) mycelial pads harvested from 40 ml of liquid medium in 250 ml Erlenmeyer flasks. During the growth period, the cultures are incubated at 27°C, and replicas are harvested at 24 h intervals following inoculation.



After a 96 h incubation period, on 10 *mM* eq. of the various substrates, Pyr-1 yields (in mg mycelia, dry weight) the following: uridine 92 mg, cytidine 100 mg, uracil 62 mg, dihydrouracil 19 mg, β -ureidopropionic acid 21 mg. See Figure 3 for comparative growth rates. On cytosine, only a trace of growth is found, and thymidine, thymine, ureidosuccinic acid, dihydroorotic acid, and β -alanine fail to support any growth. All of the compounds in the uracil degradation pathway, except β -alanine, are capable of partially satisfying the pyrimidine requirement of Pyr-1. These data indicate that in the absence of sufficient uridine, the reductive pathway is reversed to function synthetically.

⁵ F. J. DiCARLO, A. S. SCHULTZ, and A. M. KENT, *J. biol. Chem.* **199**, 333 (1952).
⁶ R. M. FINK, R. E. CLINE, and H. M. G. KOCH, *Fed. Proc.* **13**, 207 (1954). — L. L. CAMPBELL, Jr., *J. Bact.* **73**, 220 (1957); **73**, 225 (1957).
⁷ K. C. LEIBMAN and C. HEIDELBERGER, *Fed. Proc.* **14**, 243 (1955). — U. LAGERKVIST and P. REICHARD, *Acta chem. scand.* **8**, 361 (1954). — R. J. RUTMAN, A. CANTAROW, and K. E. PASCHKIS, *J. biol. Chem.* **210**, 321 (1954). — E. S. CANELLAKIS, *Fed. Proc.* **14**, 324 (1955).
⁸ H. K. MITCHELL and M. B. HOULAHAN, *Fed. Proc.* **6**, 506 (1947). — A. M. MICHELSON, M. DRELL, and H. K. MITCHELL, *Proc. nat. Acad. Sci.*, Wash. **37**, 396 (1951). — H. K. MITCHELL, *Symposium on Growth Factors*, 6th Congr. int. Microbiol. (1953), p. 75.
⁹ A. KORNBERG, *The Chemical Basis of Heredity*, Symposium of the McCollum-Pratt Institute (The Johns Hopkins Press, 1957), p. 579.
¹⁰ V. W. WOODWARD, J. R. DEZEEUW, and A. M. SRE, *Proc. nat. Acad. Sci.*, Wash. **40**, 192 (1954).



According to the pathway of uridine-5'-phosphate synthesis, Figure 2, and to the growth data presented above, Pyr-1, is genetically blocked between dihydroorotic acid and orotic acid; it grows on the latter and all subsequent compounds in the pathway, but not on the former. The products accumulated in the mycelia of Pyr-1, however, do not support this view. Mycelial extracts for chromatography are prepared by the methods of FINCHAM and BOYLEN¹¹. From these studies, it is clear that ureidosuccinic acid accumulates in the mycelia, but dihydroorotic acid does not accumulate in detectable quantities. Since ureidosuccinic acid is not detected in the medium, but only in the mycelia, it is probable that it is impermeable. The disparity between the growth data and the accumulation products, as to the exact location of the genetic block, might be due to the impermeability of dihydroorotic acid. At any rate, the genetic block is between ureidosuccinic acid and orotic acid, see Figure 2.

Evidence that the reductive pathway operates catabolically comes from analyses of wild-type. The accumulation products of aerated culture media are determined by first concentrating 1 l of medium, after 72 h of growth, to $1/25-1/50$ the original volume. Following filtration and precipitation of excess salts in the cold, the concentrate is chromatographed by the methods of

- 1 — Wild-type on min. or uridine
- 2 — Pyr-1, on 10 *mM* eq. uridine
- 3 — Pyr-1, on 10 *mM* eq. uracil
- 4 — Pyr-1, on 10 *mM* eq. ureidopropionic acid
- 5 — Pyr-1, on 10 *mM* eq. dihydrouracil

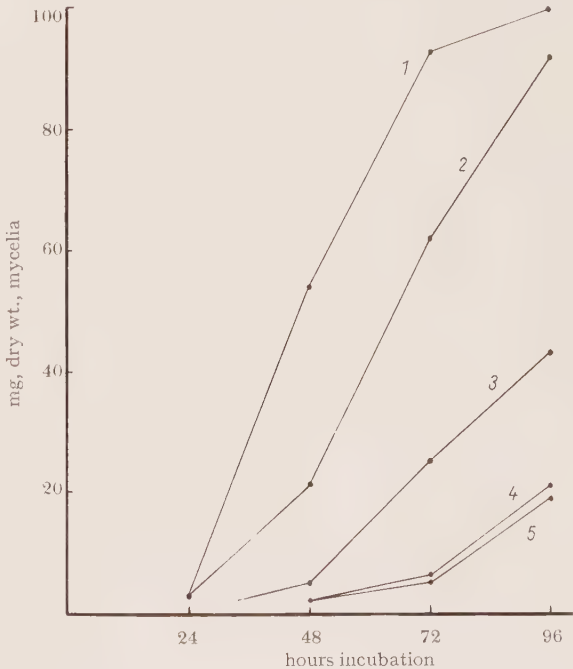


Fig. 3.—Comparative Growth Curves of Wild-type and Pyr-1 on Various Substrates

¹¹ J. R. S. FINCHAM and J. B. BOYLEN, *J. gen. Microbiol.* **16**, 138 (1957).

FINK *et al.*¹². When wild-type is cultured in minimal medium, the compounds of the reductive pathway, dihydrouracil and β -ureidopropionic acid, cannot be detected in the medium, but when grown in excess uridine these compounds accumulate. It is conjectured that during growth the uridine synthesized is used for nucleotides, but with excess uridine present, uracil arises from nucleotide degradation, and, after accumulating in sufficient quantity, is further degraded to β -alanine, NH_3 and CO_2 .

There is also evidence of a uracil pool in *Neurospora*. Wild-type, cultured in 10 mM eq. of uracil, consumes approximately 70% of the uracil during the first 96 h of incubation according to spectral analyses. It is not known at present what proportion of this is degraded and what proportion is used for nucleotide synthesis, but, when grown in minimal medium, wild-type accumulates approximately 0.1 mM eq. of uracil without any detectable accumulation of dihydrouracil and β -ureidopropionic acid. That the accumulated product is uracil can be verified by cross-feeding experiments. It has been shown with rat liver slices¹³ that the uracil $\rightarrow$ dihydrouracil reaction is the rate-limiting step of the degradation pathway; if this is so in *Neurospora*, as our preliminary evidence indicates, it would explain the existence of a uracil pool.

This work will be published in fuller detail elsewhere.

Acknowledgement. We express our gratitude to Dr. MARY B. MITCHELL for providing us with the mutant, Pyr-1 (263). These investigations were made with the aid of a research grant, RG-4561 (CS), from the National Institutes of Health, Bethesda, Maryland. Contribution No. 585, Department of Agronomy, Kansas Agricultural Experiment Station, Manhattan.

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K. D. MUNKRES, and Y. SUYAMA

Kansas State College, Manhattan, August 20, 1957.

Zusammenfassung

Der Pyrimidinbedarf der *Neurospora crassa*-Mutante Pyr-1 (263) kann durch alle beim reduktiven Abbau des Uracils durchlaufenden Zwischenprodukte, mit Ausnahme des β -Alanins, zum Teil befriedigt werden, nämlich durch β -Ureidopropionsäure, Dihydrouracil und Uracil. Wildwachsende *Neurospora* speichert nach Zuzug von Uridin in der Nährlösung β -Ureidopropionsäure und Dihydrouracil, aber nicht bei Abwesenheit von Uridin. Aus diesen Feststellungen folgt, dass der reduktive Umbau des Uracils je nach den Konzentrationsverschiebungen in der Nährlösung im aufbauenden oder im abbauenden Sinne verlaufen kann.

¹² R. M. FINK, R. E. CLINE, G. MCGAUGHEY, and K. FINK, *Analyt. Chem.* 28, 4 (1956).

¹³ P. FRITZSON, *J. biol. Chem.* 226, 223 (1957).

Variations in the Glycosidic Pattern of Anthocyanins

Part II¹

A study of the glycosidic nature of the anthocyanin plant pigments is being carried out as part of an investigation of the role of glycosidation in anthocyanin biosynthesis. The discovery of a new type of glycoside,

in which the anthocyanidin has two sugar residues in the 3-position and one in the 5-position, has been reported earlier². Other novel types of anthocyanidin glycosides have now been found in a variety of plant material. Most progress has been made with glycosides of pelargonidin (3,5,7,4'-tetrahydroxyflavylium chloride) since it is possible in most cases to determine the position of the sugar residues without recourse to detailed chemical analysis. For example, pelargonidin glycosides which have a sugar residue in the 5-position display a characteristic yellow fluorescence in ultra-violet light³.

The method of determining the position and nature of the sugar residues of anthocyanins employing the techniques of paper partition chromatography have been outlined elsewhere⁴. It consists of hydrolysing a solution of the anthocyanin, carefully purified by repeated chromatography, and identifying the aglycone and sugars by standard procedures. The number and position of the sugar residues is then obtained by controlled acid hydrolysis of the anthocyanin and examining all the simpler glycosides produced as intermediates. The comparison of R_f values with known pigments in a variety of solvent systems is also necessary for identifying new compounds. Since our earlier reports⁵, one modification has had to be introduced into the method, since it was found that arabinose is produced as an artifact during the purification of anthocyanins on Whatman No. 3 paper if solvent mixtures containing hydrochloric acid are used. The presence of this acid was considered necessary for preventing the anthocyanin fading during chromatography. This difficulty has now been overcome by replacing the hydrochloric by acetic acid, and by washing the sheets of filter paper prior to their use with dilute acetic acid. As a result, it has been necessary to revise the provisional structures of some pigments described earlier as containing arabinose. Thus, the acylated pelargonidin derivative present in *Solanum phureja* is the 3-rhamnoglucosido-5-monoglucoside and the unusual cyanidin glycoside present in the stems of *Streptocarpus spp.*, in elderberries and in the leaves of *Begonia spp.* is cyanidin-3-xyloglucoside. In the same way, the cyanidin derivative of *Dahlia variabilis*, described recently by NORDSTRÖM⁶ as the 3-glucosido-5-arabinoside, must be the 3:5-diglucoside, since this author based his identification on chromatographic methods using solvents containing mineral acid.

In all, some nine chromatographically distinct glycosides of pelargonidin have been examined, the well characterised 3-monoglucoside (callistephin) and 3:5-diglucoside (pelargonin) being available for comparison. Variation due to acylation was eliminated by subjecting pigments containing acyl groups to alkaline hydrolysis before further examination. Some of the nine glycosides fall into the 'classes' described by the ROBINSONS⁷. The majority of 3-monosides examined are identical with callistephin, but there is evidence that pelargonidin-3-monogalactoside occurs in trace amounts with cyanidin-3-monogalactoside in the leaves of the copper beech, *Fagus sylvatica*. The 3-monoglucoside and 3-monoga-

² J. B. HARBORNE, *Nature* 179, 429 (1957).

³ R. ROBINSON *et al.*, *J. chem. Soc.* 1931, 2672.

⁴ J. B. HARBORNE and H. S. A. SHERRATT, *Biochem. J.* 65, 23 P (1957).

⁵ J. B. HARBORNE, *Nature* 179, 429 (1957). – J. B. HARBORNE and H. S. A. SHERRATT, *Biochem. J.* 65, 23 P (1957).

⁶ C. G. NORDSTRÖM, *Acta chimica scand.* 10, 1491 (1956).

⁷ G. M. ROBINSON and R. ROBINSON, *Biochem. J.* 26, 1647 (1932).

¹ Part I: *Nature* 179, 429 (1957).

lactoside have very similar R_f values, and only separate distinctly when the paper is developed for at least 24 hours with a solvent mixture based on *n*-butanol.

A pelargonidin-3-rhamnoglucoside, probably the 3-rutinoside, previously identified in pink forms of *Antirrhinum majus*⁴, has also been found in *Solanum phureja*. The 3-bioside occurring in petals of *Papaver spp.*⁸ has been identified as a 3-diglucoside. It is probably the 3-gentiobioside, since it occurs with meocyanin (cyanidin-3-gentiobioside⁹) in *Papaver rhoeas*. Two further pelargonidin derivatives, one found in *Tritonia*, variety 'Prince of Orange', and the other in *Primula sinensis*¹⁰, differ chromatographically from the above pigments, but must also be considered to be a 3-rhamnoglucoside and a 3-diglucoside respectively. These two cases of isomeric forms of the same glycoside are presumably due to difference in the linkage between the sugar residues of the disaccharides concerned. Indeed, assuming that the combined glucose has the β -D-pyranoside configuration, four isomeric 3-diglucosides of pelargonidin may theoretically occur in nature.

The structure of the pelargonidin-3-rhamnoglucosido-5-monoglucoside of *S. phureja* mentioned previously has been confirmed by identifying the 3-monoglucoside, the 3-rhamnoglucoside, the 3:5-diglucoside and the 5-monoglucoside of pelargonidin as products of its partial acid hydrolysis. Another example of this new type of glycoside is the pigment present in the skin of radishes, *Raphanus sativum*. It is an acylated derivative of pelargonidin 3-diglucosido-5-monoglucoside. On partial hydrolysis, it gives the 3-gentiobioside, the 3:5-diglucoside and the 3- and 5-monoglucosides. Two other novel types of pelargonidin glycoside must be mentioned. One of these occurs in *Primula sinensis*¹⁰, with the 3-monoglucoside and a 3-diglucoside of pelargonidin and appears to be a 3-triglucoside, since only the first two simpler pigments can be detected during acid hydrolysis. Although flavonols with three sugar residues attached at a single position (i.e. the 3-position) have recently been found in nature¹¹, no anthocyanins of this type have been recorded before.

The other novel glycoside occurs with pelargonidin-3-gentiobioside in *Papaver orientale*. It is remarkable in being distinctly lighter orange in colour than any of the other naturally occurring glycosides of pelargonidin. Indeed, its maximum in the visible spectrum is 499 m μ when measured in methanol, containing a trace of hydrochloric acid. Other pelargonidin glycosides have λ_{max} at 505 m μ in the same solvent. On acid hydrolysis, it gives only glucose and pelargonidin. Four non-fluorescent glycosides are produced during this hydrolysis. Two were identified, namely the 3-gentiobioside and the 3-monoglucoside. It follows that the original glycoside must have two glucose residues in the 3-position and one in the 7- or 4'-position. Up to now, it has always been assumed that anthocyanins only contained sugars substituted in the 3- and 5-positions.

Other results indicate that a similar range of glycosides of the other five commonly occurring anthocyanidins are present in nature. For example, different forms of the cultivated potato are pigmented with the six common anthocyanidins as the 3-diglycosido-5-monoglycoside

acylated with *p*-coumaric acid. Although some details of the structure of these pigments remain to be determined, it is apparent from these preliminary results that anthocyanins occur as a range of glycosidic forms comparable with the variation encountered in the flavonol series¹².

The co-occurrence of pelargonidin mono-, di- and triglycosides in *Primula sinensis*, and of di- and triglycosides in *Papaver orientale* and *Solanum phureja* is significant. It appears from these and other results that a number of biosynthetic steps are involved in the glycosidation of anthocyanidins in nature. Genetical evidence supports this view since single gene differences have been related to changes in the glycosidic pattern of the anthocyanins in some plant species¹³. It seems, then, that single sugar residues are linked one at a time to the pigment molecule or precursor rather than that a preformed di- or trisaccharide is attached directly in one step.

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John Innes Horticultural Institution, Bayfordbury, Hertford (Herts), August, 28, 1957.

Zusammenfassung

Neun Glykoside des Pelargonidins wurden durch papierchromatographische Methoden gekennzeichnet. Es war notwendig, die Methode der Zuckeridentifizierung abzuändern, um die Bildung des Kunstprodukts Arabinose zu vermeiden. Einige der neun Glykoside gehören zu neuen Sorten von Anthocyanidinglykosiden, die bisher noch nicht in der Natur entdeckt waren. Die dadurch erklärte Variation im Glykosidformelbild der Anthocyane wird in bezug auf ihre Biosynthese diskutiert.

¹² T. A. GEISSMAN and E. HINREINER, Bot. Rev. 18, 77 (1952).

¹³ J. B. HARBORNE, Nature 179, 429 (1957). – W. J. C. LAWRENCE, Heredity (in press). – G. H. BEALE, J. R. PRICE, and R. SCOTTMONCRIEFF, J. Genet. 41, 65 (1940). – G. A. L. MEHLQUIST and T. A. GEISSMAN, Ann. Mo. bot. Gdn 34, 39 (1947).

Gibberellenic Acid, a By-product of Gibberellic Acid Fermentation

Recently, CROSS *et al.*¹ have proposed a structure (I) for gibberellic acid and have shown that the products of successive acid degradation, *allo*-gibberic and gibberic acid, possess the structures II and III. In our laboratories gibberellic acid, isolated² from cultures of *Fusarium moniliforme* and crystallized from ethyl acetate, was found to contain varying amounts of a by-product readily detectable by means of its strong absorption in the ultraviolet region as well as by its immobility on paperchromatogram. Using a butanol-ammonia system², for example, it remains at the point of application while gibberellic acid moves with an R_f value of 0.4. This by-product, for which we propose the name gibberellenic acid, was first obtained as a molecular complex with 2

⁸ G. M. ROBINSON and R. ROBINSON, Biochem. J. 25, 1687 (1931).

⁹ K. E. GROVE, M. INUBUSE, and R. ROBINSON, J. chem. Soc. 1608 (1934).

¹⁰ H. S. A. SHERRATT, Nature (in press) (1957).

¹¹ Y. TAKINO, H. IMAGAWA, and H. TOSHIDA, J. agric. chem. Soc. Japan 28, 182 (1954).

¹ B. E. CROSS, J. F. GROVE, J. MACMILLAN, and T. P. C. MULLHOLLAND, Chem. Ind. 1956, 954.

² N. TAKAHASHI, H. KITAMURA, A. KAWARADA, Y. SETA, M. TAKAI, S. TAMURA, and Y. SUMIKI, Bull. agric. chem. Soc. Japan 19 (4), 267 (1955).

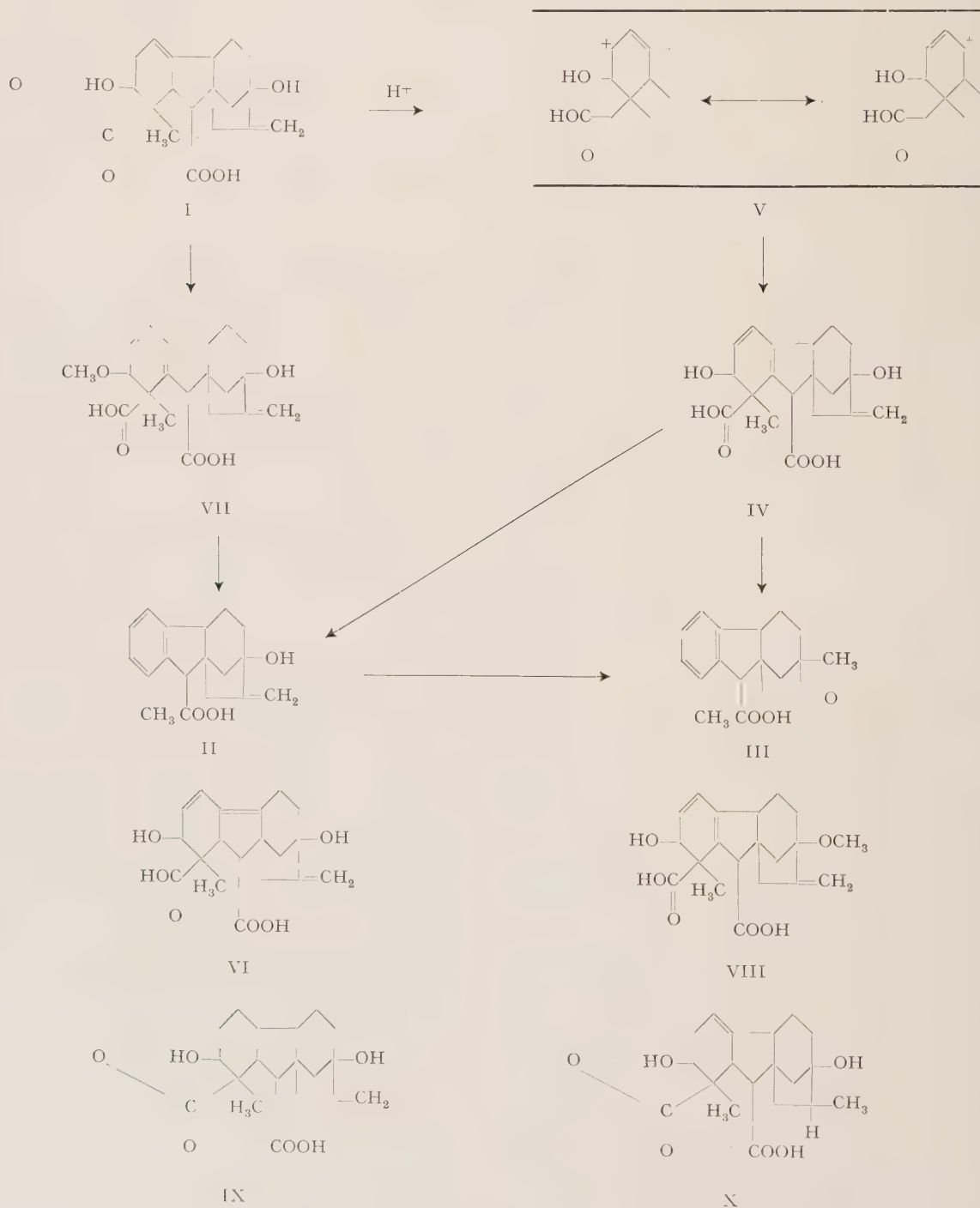
moles of gibberellic acid. Digestion of this complex with hot chloroform followed by recrystallization of the insoluble residue from ethyl acetate gave gibberellenic acid (m.p. 185°, gas evolution), a dicarboxylic acid with the same composition as gibberellic acid (Analysis. Calculated for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40; mol. weight, 346. Found: C, 66.16; H, 6.58; mol. weight by electrometric titration, 354). In the pea elongation test³ gibberellenic acid was found to be devoid of biological activity.

In contrast to gibberellic acid which is transparent between 220 and 400 $m\mu$, gibberellenic acid strongly absorbs at 253 $m\mu$ ($\epsilon = 19,200$). Sodium borohydride in

³ P. W. BRIAN, G. W. ELSON, H. G. HEMMING, and M. RADLEY, J. Science Food Agric. 5, 602 (1954).

methanolic solution does not affect this absorption maximum, but 2 moles of hydrogen are taken up rapidly when gibberellenic acid is reduced with palladium catalyst in ethanol. The resulting solution has become transparent at 253 $m\mu$. With platinum oxide as the catalyst a third mole of hydrogen is taken up slowly.

Gibberellenic acid appears to be an intermediate in the conversion of gibberellic acid to *allo*-gibberic (and gibberic) acid as evidenced by the following observations. Solutions of I in dilute hydrochloric acid (0.1–1 *N*) or in methanolic sulfuric acid at room temperature develop absorption at 253 $m\mu$. In 1% methanolic sulfuric acid this absorption attains in about 6 h a value corresponding to a 90% conversion to gibberellenic acid



and then remains at this level. In aqueous solution under optimum conditions the maximum value attained corresponds to approximately a 50% conversion and then slowly decreases until the absorption approaches that of *allo*-gibberic acid (max. = 266 m μ , ϵ = 320)⁴. Furthermore, gibberellenic acid yields *allo*-gibberic and gibberic acid when treated under the acidic conditions described⁴ for the preparation of these two acids from I.

The above observations strongly indicate that gibberellenic acid is an artifact produced from I by acid catalysis during the fermentation and/or isolation process. Accepting the proposed structure¹ for gibberellic acid (I), gibberellenic acid may be formulated as IV, its formation from I presumably proceeding by way of the carbonium ion intermediate (V)⁵. No strictly analogous model for comparison of ultraviolet absorption appears to be available but the observed absorption of IV is not incompatible with the values reported for diene systems⁶. The resistance of the tetra-substituted double bond in IV towards hydrogenation (see above) is not surprising and finds its parallel in the observed resistance to catalytic reduction of an analogous double bond in $\Delta^{8,9}$ -bicyclo(4.3.0)nonene-5,6-dicarboxylic⁷. Although the evidence presented here does not rule out the alternate structure (VI) for gibberellenic acid, the ready conversion of this acid by decarboxylation and dehydration to the aromatic *allo*-gibberic acid (II) supports structure IV.

Although the data reported here support the contention that gibberellenic acid (IV) is derived from I by acid catalysis, the conversion of I to IV in aqueous acid on a preparative scale was not feasible because of the low solubility of I and the formation of further degradation products under these conditions. On the other hand, acid methanolysis followed by neutralization with methanolic sodium methoxide provided a new crystalline dibasic acid (m.p. 188–190°, gas evolution) which likewise has an absorption maximum at 253 m μ (ϵ = 19,000). This acid was recovered unchanged after a 12 h treatment with 1 N sodium hydroxide. This observation together with the analytical data (Calculated for C₂₀H₂₄O₆: C, 66.65; H, 6.71; O–CH₃(1), 8.61; mol. weight, 360. Found: C, 66.11; H, 7.25; O–CH₃, 7.89; mol. weight by electrochromic titration, 360) allow the formulation of this acid as the methyl ether of gibberellenic acid (VII). The alternate structure (VIII) can be ruled out since its formation requires an unlikely carbonium ion intermediate. That this methyl ether-acid is correctly represented by VII was demonstrated by its conversion to *allo*-gibberic acid (II), employing the mild acidic conditions⁴ which effect the conversion of I to II. Vigorous acid treatment⁴ of VII yields gibberic acid (III). The direct conversion of IV to VII using methanolic sulfuric acid could not be realized indicating that the conversion of I to VII does not involve IV as an intermediate.

Gibberellin A₁ has been reported⁸ to be a dihydrogibberellic acid having one double bond and should

therefore be IX or X. As a sample of gibberellin A₁⁹ in acidic solution did not develop the typical absorption at 253 m μ , it must possess structure IX. This same structure has recently been proposed by SUMIKI *et al.*⁸ on the basis of ozonolysis experiments.

Acknowledgment.—Helpful discussions with Dr. C. C. PRICE and Dr. R. B. TURNER are gratefully acknowledged.

KOERT GERZON, HAROLD L. BIRD, JR., and DON O. WOOLF, JR.

The Lilly Research Laboratories, Indianapolis, Indiana, July 30, 1957.

Zusammenfassung

Unter den Fermentationsprodukten von *Fusarium moniliforme* findet sich neben der bekannten Gibberellinsäure als Nebenprodukt die Gibberellensäure. Identifizierung und Charakteristika dieser Säure (IV) werden beschrieben. Für Gibberellin A₁ wird die Struktur (IX) angegeben.

⁹ We thank Dr. F. H. STODOLA of Peoria, Illinois, for the generous gift of a sample of pure gibberellin A₁.

Release of Bradykinin as Related to the Esterase Activity of Trypsin and of the Venom of *Bothrops jararaca*

In a previous paper¹ we have shown that the bradykinin releasing activity of the venom of *Bothrops jararaca* is not related to its proteolytic activity on casein. Two apparently distinct proteolytic activities were demonstrated in the venom depending upon their different heat tolerance. While the activity on casein was found to be easily destroyed on a few minutes heating in boiling water, the remaining esterase activity on benzoyl-L-arginine methyl ester (BAME) proved to be more thermostable and only partially destroyed². As shown by SCHWERT *et al.*³ trypsin besides its proteolytic activity on casein also displays esterase activity on BAME, the latter being correlated to its amidase activity on benzoyl-L-arginine amide⁴. The venom of *Bothrops jararaca* has also been shown to act on casein and the benzoyl-L-arginine ethyl ester⁵. It therefore seems possible that the common mediator for bradykinin release of both trypsin and the snake venom may be their respective esterase activities. In the present work we have shown that such a correlation can be demonstrated. If trypsin inhibitor is removed by applying the denatured plasma as a substrate a direct relationship is found between the bradykinin releasing effect of trypsin and the heated venom of *Bothrops jararaca* when compared with their respective esterase activities on BAME.

Heating a solution of the venom in a boiling water bath for 1–3 min¹ was enough to destroy completely its

⁴ B. E. CROSS, J. chem. Soc. 1954, 4670.

⁵ This transformation closely resembles the acid catalyzed conversion of *ψ*-santonin to *ψ*-santonin acid. — N. M. CHOPRA, W. COCKER, J. T. EDWARD, T. B. H. McMURRY, and E. R. STUART, J. chem. Soc. 1956, 1828 and other references listed.

⁶ L. L. FIESER and M. FIESER, *Natural products related to Phenanthrene* (Reinhold Publishing Corporation, New York 1949), p. 185.

⁷ A. T. BLOMQUIST, J. WOLINSKY, Y. C. MEINWALD, and D. F. LONGONE, J. Amer. chem. Soc. 78, 6058 (1956). — We thank Dr. BLOMQUIST for the generous gift of this model compound.

⁸ Y. SETA, H. KITAMURA, N. TAKAHASHI, and Y. SUMIKI, Bull. agric. chem. Soc. Japan 21, 73 (1957). This structure has recently been confirmed by Dr. MAC MILLAN and his group. (Personal communication to K.G.)

¹ U. HAMBERG and M. ROCHA E SILVA, Arch. int. Pharmacodyn. 110, 2 (1957).

² U. HAMBERG and M. ROCHA E SILVA, Arch. int. Pharmacodyn. 110, 2 (1957); Proc. 20th Int. physiol. Congr. Brussels 390 (1956).

³ G. H. SCHWERT, H. NEURATH, S. KAUFMAN, and J. E. SNOKE, J. biol. Chem. 172, 221 (1948).

⁴ M. BERGMANN, J. S. FRUTON, and H. POLLOK, J. biol. Chem. 127, 643 (1939).

⁵ C. R. DINIZ and H. F. DEUTSCH, J. biol. Chem. 216, 17 (1955).

proteolytic activity on casein and reduced to about 50% its esterase activity on BAME. However if heating was continued a slow but continuous drop in the residual esterase activity was observed. Complete destruction was obtained after a prolonged heating for 90 min in a boiling waterbath. This would indicate (Fig. 1) that we are dealing with a complex enzymatic mixture and that at least three different activities are involved: (1) A thermolabile activity as measured on casein; (2) a thermolabile esterase activity, possibly connected with activity (1), and (3) a more thermostable esterase component, concerned with the release of bradykinin.

The capacity of the venom of releasing bradykinin when incubated with fresh plasma, first increased after a short heating of the venom, concomitantly with a drop in proteolytic activity, until a maximum is attained after 1–3 min of heating the venom. Thereafter the yield decreased in parallel with the esterase activity. The initial increase in the yield of bradykinin might be explained by the fact that the bradykinin destroying activity of the venom disappears with its proteolytic activity on casein.

The clotting power of the venom decreased sharply when heat was applied. There was a marked initial drop after 1 min heating, to about 30% of the initial value, followed by a slow decrease in parallel with the relatively thermostable esterase activity (Fig. 1). It can therefore be concluded that this residual esterase activity correlated to bradykinin release also is effective in bringing about the coagulation of the blood.

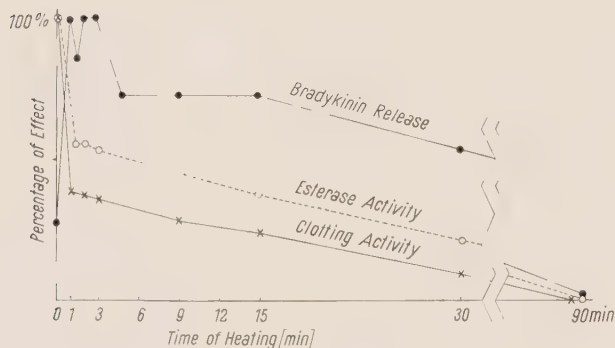


Fig. 1.—Effect of heat denaturation upon the bradykinin releasing and clotting activities of the venom of *Bothrops jararaca*, as related to its esterase activity on BAME. In abscissae, time in minutes of heating a 0.5% saline solution of the venom at pH 6 in a boiling waterbath. Temperature at the end of heating periods 82–95°C. The proteolytic activity on casein as measured by absorption in U.V. decreased to zero after 1 min heating (the curve is not presented in this graph).

After 3 min heating of the venom residual esterase activity was found to be about $\frac{1}{20}$ of that of trypsin. Since destruction of bradykinin by the venom was prevented by the heating and since the bradykinin destroying effect of plasma, as well as the trypsin inhibitor also were removed by heat denaturation of the plasma², a comparison of the esterase activity with the bradykinin releasing effect of the venom was made possible. The experiments were performed by applying equipotent esterase activities (BAME) of trypsin and heated venom on denatured plasma. Equal amounts of bradykinin were found to be released with both agents showing a parallelism between the relatively thermostable esterase activity of the venom and its bradykinin releasing effect. A striking difference was found regard-

ing the specificity of the proteolytic activity of both agents. Although the concentration of split products with absorption in U.V. light increases with time and in parallel with bradykinin release when trypsin is used, no measurable amounts of protein split products are obtained with the heated venom. In another series of experiments, increasing concentrations of venom and trypsin were incubated with denatured plasma, and the ratios of their respective esterase activity (BAME) were determined (Fig. 2). In each case equal bradykinin release was obtained with both agents.

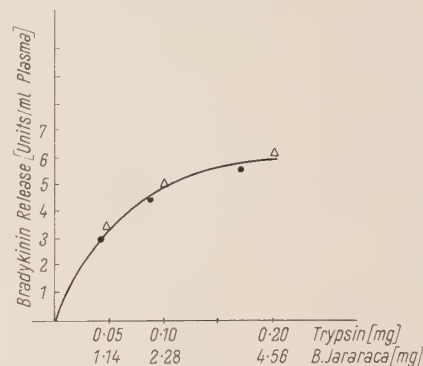


Fig. 2.—Bradykinin released from denatured plasma proteins with increasing equipotent (BAME) esterase concentrations of trypsin and the heated venom (mg/ml plasma).

These findings agree with those described by HOLTZ and RAUDONAT⁶ who were able to separate by fractionation with ammonium sulphate a thrombin-like fraction (Koagulin) from a proteolytic fraction which activates prothrombin. The bradykinin releasing activity was present in the non-proteolytic 'Koagulin' fraction of the *Bothrops* venom.

In conclusion: Fractionation by heat of the venom of *Bothrops jararaca* gives a fraction with the specific activity on benzoyl-L-arginine methyl ester (BAME) which can be directly correlated to bradykinin release from fresh or denatured plasma and with the clotting power on fresh plasma. When compared with the effect of trypsin equal ratios are obtained with the heated venom for the bradykinin releasing effect and the esterase activity on BAME. The high specificity of the venom in releasing bradykinin would indicate that bradykinin is held in a terminal position in the precursor molecule.

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Department of Biochemistry and Pharmacodynamics,
Instituto Biológico, São Paulo (Brazil), June 3, 1957.

Zusammenfassung

Die proteolytische Aktivität des Giftes von *Bothrops jararaca* wird durch Erhitzen leicht zerstört und dabei eine Esterase mit grösserer Hitzeresistenz abgetrennt. Nach Hitzefraktionierung des Giftes steht die Aktivität dieser Esterase in direktem Verhältnis zum abgegebenen Bradykinin und zur Gerinnung des frischen Plasmas.

⁶ P. HOLTZ and H. W. RAUDONAT, Arch. exp. Path. Pharmacol. 229, 113 (1956).

⁷ Fellow of the C.A.P.E.S., Rio de Janeiro, Brazil.

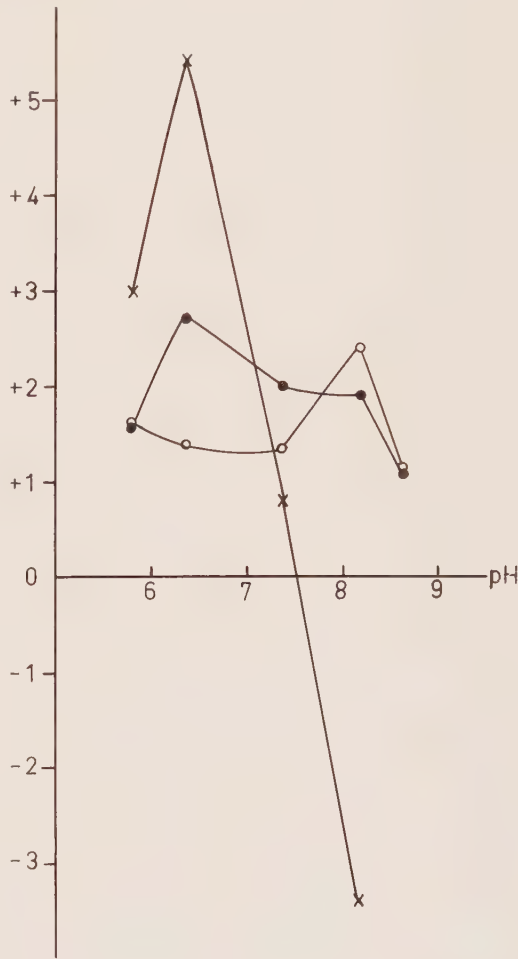
On the Adenosinetriphosphatase Activity of the Particulates of the Egg of the Sea Urchin *Paracentrotus Lividus*

The preparation of the particulates (mitochondria) from homogenates of eggs of *Paracentrotus lividus*, using sucrose concentrations from 0.25 to 0.44 M, results in a yellowish sediment at the bottom of the centrifuge tube overlaid by a red fluffy layer. This sediment can be further purified by resuspending it in 1 M sucrose and centrifuging at high speed (MONROY¹). In this way most of the pigmented fluffy layer floats on the surface of the sucrose and the sediment shows only an orange-yellow colour. The light red particulates of the fluffy layer were considered to be identical with the pigment granules of the egg which had been previously isolated with a similar technique (MONROY and DE NICOLA²). The sedimented granules were considered to be mitochondria and they were found to be endowed with protease (MAGGIO³) and adenosinetriphosphatase (ATPase) (MONROY¹) activities. The study of the ATPase activity in such granules was mainly centered around its changes upon fertilization and was carried out under standard conditions, using veronal buffer at pH 8.0 and Mg⁺⁺ as activator.

It was the intention of the present writer to study in some detail the properties of the latter enzyme in unfertilized and fertilized eggs of *Paracentrotus lividus*. First of all pH-activity curves were run, especially in consideration of the recent findings of MYERS and SLATER⁴ on the presence in rat liver mitochondria of four different ATPases, which can be distinguished from each other by their pH optima, activators and inhibitors. However, when this work was undertaken, irregular results were often obtained and the impression was soon gained that they may somehow depend on the amount of the so-called red contaminant in the mitochondria sediment. It was then decided to investigate this point and a series of experiments has been made with unfertilized eggs using preparations of (a) mixed red + yellow particulates, i.e. unpurified sediment, (b) yellow sediment free as much as possible of the red granules, (c) red particulate only. For the preparation of the particulate fractions, the directions given by MONROY¹ were followed. The experiments were run at pH from 5.8 to 8.6 and for each preparation two separate series of determinations were made, one without activator and one with 4 μM of Mg⁺⁺ as activator. Tris(hydroxymethyl)amino-methane-maleate buffer has been used over the whole range of pH. Preliminary experiments gave evidence that the results may vary to a certain extent when different buffers are employed.

By plotting the difference curves obtained by subtracting the values of the activities without activator from those with Mg⁺⁺, the results are obtained which are illustrated in the accompanying diagram. They show that the unpurified, i.e. red + yellow particulates, exhibit two maxima of Mg-activation, one at pH 6.4 and the other at pH 8.2. When a good purification is achieved and the yellow sediment is well freed of the red granules, then only the 6.4 maximum is found. It seems, furthermore, that, in these preparations at pH higher

than 7.4, Mg acts as an inhibitor. On the other hand, preparations of the red granules only show the 8.2 activation maximum. It must be added at the point that at pH 8.0 an activation by Mg on the ATPase of the yellow granules has been described by MONROY¹ working in veronal buffer; and it has been confirmed in the course of the present experiments. This point requires elucidation.



Mg-activation of the ATPases of the particulates of unfertilized eggs of *Paracentrotus lividus*. ●—● unpurified, i.e. red + yellow particulates; x — x yellow particulates; ○—○ red particulates. Difference curves obtained as described in the text.

Observations at the electron microscope on smears of these preparations do not allow one to recognize any difference between the red and the yellow granules. Observations by GHIRETTI-MAGALDI and MAGGIO (personal communication) in which the particulates of the sea urchin egg have been fractionated in a density gradient, have shown that the cytochrom system is localized exclusively in the red granules.

These observations show that the particulate system of the sea urchin egg is a heterogeneous population. Furthermore, these observations raise the question of the significance of the carotenoid pigments contained in these granules (DE NICOLA and MONROY-ODDO⁵) both from the physiological and the morphogenetic

1 A. MONROY, J. cell. comp. Physiol. (in press).

2 A. MONROY and M. DE NICOLA, Exper. 8, 29 (1952).

3 R. MAGGIO, J. cell. comp. Physiol. (in press).

4 D. K. MYERS and E. C. SLATER, Nature 179, 363 (1957).

5 M. DE NICOLA and A. MONROY-ODDO, Exper. 8, 187 (1952).

point of view (see MONROY and DE NICOLA²; GUSTAFSON⁶).

This investigation has been supported by a Grant from Consiglio Nazionale delle Ricerche to the Laboratory of Comparative Anatomy.

C. M. B. RICOTTA

Laboratory of Comparative Anatomy, The University of Palermo (Italy), July 25, 1957.

Riassunto

I particolari delle uova vergini di riccio di mare possono essere separati, a mezzo della centrifugazione differenziale, in due frazioni, una fortemente ed una scarsamente pigmentata. La prima mostra una attività ATPasica attivata da Mg con un massimo a pH 8.2; il massimo della seconda è invece a pH 6.4. Nelle preparazioni contenenti i due tipi di particolari si ritrovano i due massimi.

⁶ T. GUSTAFSON, Int. Rev. Cytol. 3, 277 (1954).

Produktion von leukozytenemigrationsfördernden Stoffen durch grampositive Keime *in vitro*

Grampositive und gramnegative Bakterien, mit Leukozyten in Kontakt gebracht, bewirken Emigrationsförderung der Leukozyten¹. Es gelingt, wie wir früher beschrieben haben, aus gramnegativen Bakterien und ihrer Kulturflüssigkeit emigrationsfördernde Lipopolysaccharide zu isolieren. Dieses gelang bisher nicht bei grampositiven auf Bouillon oder synthetischen Nährböden gezüchteten Bakterien, weder isolierte Polysaccharide noch Fraktionen aus Nährflüssigkeit sind wirksam². Andererseits konnte der eine von uns früher zeigen, dass bei Züchtung von Streptokokken auf Plasmanährboden leukozytenemigrationsfördernde sterile Kulturfiltrate gewonnen werden können³. Es erschien uns wichtig, nochmals den Versuch zu machen, aus Kulturen von grampositiven Bakterien leukozytenemigrationsfördernde Stoffe zu gewinnen, da die Bakterien selber eine solche Wirkung besitzen und auch bei Infekt im tierischen Organismus eine chemotaktische Wirkung mit Abszessbildung gerade bei diesen Bakterien von besonderer Wichtigkeit ist. Auf Grund der Befunde mit Züchtung von Bakterien auf Plasmanährböden und in Erwägung der im tierischen Organismus vorliegenden Verhältnisse konnte mit der Möglichkeit gerechnet wer-

den, dass diese Bakterien nur aus tierischem Material leukozytenemigrationsfördernde Stoffe freisetzen oder bilden können. Wir haben deshalb unsere Versuche unter Zusatz verschiedener steriler Organe wiederholt (Knorpel von Huhn und Kaninchen, Herz von Maus und Leber von Kaninchen) und die leukozytenemigrationsfördernde Wirkung der von diesen Kulturen erhaltenen Filtrate quantitativ festgestellt.

Material. (Beispiel) Die knorpeligen Teile der Brustbeine ausgewachsener Kaninchen wurden herauspräpariert und in kleine Stückchen von etwa 1 mm Kantenlänge zerschnitten. Diese wurden in eine Glucosebouillon im Verhältnis von etwa 100 mg Knorpel/1 cm³ Bouillon gebracht. Als Bakterium wurde der *Streptococcus pyogenes haemolyticus* SH (lyophilisiert) verwendet. Das Lyophilisat wurde 24 h in Bouillon bebrütet, die Bouillonverdünnung wurde Mäusen gespritzt. 24 h nach Injektion wurde eine kranke Maus getötet und ihr Herz in Bouillon gebracht. Diese 24 h alte Bouillon wurde zum Versuch verwendet.

Methode. 4 Erlenmeyerkolben wurden mit Bouillon-Glucose beschickt. 1 diente als Bouillonkontrolle, 2 wurde mit je 2 Tropfen Streptokokkenbouillon pro cm³ Bouillon beimpft. 3 wurden die geschnittenen Knorpelstückchen zugegeben im Verhältnis 1:10, 4 enthielt Bouillon, Knorpel (im gleichen Verhältnis wie Röhrchen 3) und 2 Tropfen/cm³ Streptokokkenbouillon. Brutschrank 37°C unter leichter Bewegung. Nach 4 bzw. 6 Tagen wurden zur Kulturkontrolle Ausstriche gemacht, der Kolbeninhalt wurde darauf 1 h im Wasserbad erhitzt und zentrifugiert. Die überstehende Flüssigkeit wurde mit Tyrode verdünnt den Leukozytenkulturen überschichtet (Leukozytenauswanderung: Methode Arch. exp. Path. Pharm. 224, 104 (1955)). Alle Versuche wurden 6mal wiederholt. Pro Bouillonverdünnung wurden je 5 Leukozytenkulturen verwendet.

Das Ergebnis der Untersuchungen ist in untenstehender Tabelle zusammengefasst.

Durch Dialysieren unter sterilen Bedingungen lässt sich die Wirksamkeit der Streptokokken-Knorpel-Kulturbouillon leicht steigern. Eine Wirksamkeit der Kontrollen tritt auch unter diesen Bedingungen nicht auf.

Es ergibt sich somit, dass die Bildung von leukozytenemigrationsfördernden Stoffen durch Streptokokken bei Zusatz von gewissen Organen zur Kulturbouillon erheblich gesteigert werden kann. Auf Grund der vorliegenden Versuche kann somit die Diskrepanz zwischen der Wirksamkeit lebender Bakterien und dem Fehlen der Wirkung bei abgetöteten und in rein synthetischer Nährflüssigkeit gezüchteten dahin aufgeklärt werden, dass grampositive Bakterien nur aus tierischem Material leukozytenemigrationsfördernde Stoffe bilden oder freisetzen. Die wirksamen leukozytenemigrationsfördernden

¹ R. MEIER, Z. ges. exp. Med. 87, 283 (1933).
² R. MEIER und B. SCHÄR, Exper. 9, 93 (1953).
³ R. MEIER, Helv. chim. Acta 24, 134/E/(1941).

Wirkung von *Streptococcus-pyogenes-haemolyticus*-Kulturbouillon mit und ohne Zusatz von Knorpelgewebe auf die Leukozytenauswanderung *in vitro*.

Verdünnung der Bouillon 1 h 100°C	Bouillon	Bouillon + Knorpel	Bouillon + Streptococc.	Bouillon + Streptococc. + Knorpel
1:10	Ø	Ø	(+)	+++
1:100	Ø	Ø	Ø	++
1:500	Ø	Ø	Ø	+

Ø = keine Auswanderungsförderung
+ = leichte Auswanderungsförderung
++ = mässige Auswanderungsförderung
+++ = starke Auswanderungsförderung

Stoffe sind hitzestabil und nicht dialysierbar. Sie dürften für die Entzündungsreaktionen, welche durch gram-positive Bakterien ausgelöst werden, von Bedeutung sein. Es ist weiterhin möglich, dass die Entstehung von organspezifischen Autoantikörpern mit ihrer Bildung in Zusammenhang steht. Abklärung ihrer chemischen Konstitution und ihrer pharmakologischen Wirkung im einzelnen dürfte weitere Aufschlüsse geben.

R. MEIER und B. SCHÄR

Forschungslaboratorien der CIBA Aktiengesellschaft, Pharmazeutische Abteilung, Basel, 23. September 1957.

Summary

Streptococcus pyogenes haemolyticus grown in glucose broth is capable of producing or liberating a heat-stable factor of high molecular weight which stimulates the emigration of leucocytes *in vitro*, only if certain animal organs are present.

The Exudative Diathesis Produced by Torula Yeast*

The development of exudative diathesis in chicks was first produced by vitamin E deficient diets to which was added an easily oxidizable fat such as cod liver oil¹. When the vitamin E deficient diet was fat-free, the symptom did not appear².

SCOTT, HILL, NORRIS, DOBSON, and NELSON³ have described the development of exudative diathesis by means of diets containing about 60% (dry) torula yeast as the only source of protein, and without added fat. Similar results have been reported by BIERI, POLLARD, and BRIGGS⁴ using alcohol-extracted torula yeast. These authors were of the opinion that the diets used in their experiments did not contain fat in such a quantity that it could be responsible for the development of the symptom, and therefore held that easily oxidizable fat is not necessary for the occurrence of exudative diathesis.

We have had the opportunity to carry out similar feeding experiments with chicks receiving diets with torula yeasts of the same kinds ('1N' and '3N' from Lake States Yeast Corporation, Rhinelander, Wisconsin) as those used by SCOTT *et al.* We thereby confirmed the observation that exudative diathesis occurs in chicks fed such diets without added fat.

However, we found a considerable content of fat and easily oxidizable fatty acids in the torula yeast. Torula yeast '1N' was found to contain 4.5% total fatty acids, 41.8% of which were dienoic and 5.7% trienoic. The corresponding figures for torula yeast '3N' were 5.3% total fatty acids with 44.7% dienoic and 2.6% trienoic.

* We are grateful to Lake States Yeast Corporation, Rhinelander, Wisconsin, for supply of the torula yeast used in these experiments.

¹ H. DAM and J. GLAVIND, *Nature* 142, 1077 (1938).

² H. DAM, *Proc. Soc. exper. Biol. Med. N. Y.* 52, 285 (1943).

³ M. L. SCOTT, F. W. HILL, L. C. NORRIS, D. C. DOBSON, and T. S. NELSON, *J. Nutrition* 56, 387 (1956).

⁴ J. G. BIERI, C. J. POLLARD, and G. N. BRIGGS, *Fed. Proc.* 16, 381 (1957).

The total amount of fatty acids in the yeast was found after alkaline hydrolysis. Extraction after acid hydrolysis alone gave a somewhat lower figure.

Dr. BIERI of the National Institutes of Health, Bethesda, Md., has generously sent us two samples of his torula yeast, one untreated and the other alcohol extracted. We found that the untreated yeast contained 4.8% total fatty acids, whereas the alcohol extracted yeast contained 2.7%. The contents of dienoic fatty acids in the total fatty acids of the two samples were 44.8 and 45.3%, respectively; the contents of trienoic were 4.0% and 3.6%.

In our experiments we have found that diets with as little as 10% of torula yeast may produce exudates, although to a much lesser extent than diets with 60% of this yeast. In certain earlier experiments⁵ very pronounced exudates were produced with diets containing 5% lard, whereas the corresponding fat-free diet gave no such symptoms. Although the lard used at that time was not analyzed for individual fatty acids, it is apparent from later analyses of lard, that 5% of lard must have contributed about as much dienoic and trienoic acids as 10% of torula yeast has. 60% of torula yeast will contribute roughly the same amount of dienoic and trienoic acids as will 30% of lard.

We, therefore, do not consider the experiments described by the aforementioned American authors as proof for the assumption that easily oxidizable fat is not necessary for the occurrence of exudative diathesis, although we agree with them with respect to the usefulness of torula yeast in the study of exudative diathesis in chicks.

It may be added that a type of yeast (Fleischmann 50 B) which in our experiments did not produce exudative diathesis contained 3.8% of total fatty acids, but only 0.3% of this amount was dienoic. The presence of tri-, tetra-, penta-, and hexaenoic acids could not be demonstrated with certainty.

The exudative diathesis produced by torula yeast diets without added fat is very pronounced. Exudates occur in fat tissue and in muscles and skin, as is the case when cod liver oil-casein diets are used. The exudates originating from muscles may be even more pronounced with torula yeast diets. Torula yeast diets also produced peroxidation of body fat as previously found with casein diets containing cod liver oil⁶ and lard⁷. White striation of breast muscles⁸, and a few cases of encephalomalacia also occurred when exudate-producing torula yeast diets were fed.

During the course of the experiments described here we received a personal communication from Dr. E. L. R. STOKSTAD of The American Cyanamid Company, Research Division, and shortly thereafter one from Dr. K. SCHWARZ, National Institutes of Health, Bethesda, Md., informing us that selenium as selenite prevents the exudative diathesis in chicks, when this element is fed in amounts below the toxic level.

Using 60% torula yeast diets we have confirmed this very important finding, and may add that at the level of 5 ppm Se as pure SeO₂ (7 ppm) did not prevent encephalomalacia, even though the exudative diathesis and

⁵ H. DAM, *J. Nutrition* 27, 193 (1944).

⁶ H. DAM and H. GRANADOS, *Acta physiol. scand.* 10, 162 (1945).

⁷ H. DAM, INGE PRANGE, and E. SØNDERGAARD, *Acta pharmacol. toxicol.* 8, 1 (1952).

⁸ H. DAM, INGE PRANGE, and E. SØNDERGAARD, *Acta pathol. microbiol. scand.* 31, 172 (1952).

the peroxidation of depot fat were suppressed. On a diet with 30% casein and 30% lard, which produced encephalomalacia as the main symptom, the incidence of encephalomalacia was uninfluenced by the presence of 7 ppm of SeO_2 .

On a 30% casein, 10% cod liver oil diet which produced about an equal incidence of encephalomalacia and exudative diathesis, only the last mentioned symptom was prevented by 7 ppm of SeO_2 .

The finding of the protective effect of selenium on exudative diathesis may throw light upon certain older observations from our laboratory⁹, according to which a certain cystine preparation gave protection against exudative diathesis (not against encephalomalacia) when fed at a level of 0.5%. This observation could not be confirmed with later supplies of cystine from other sources. As emphasized by SCHWARZ, cystine may sometimes be contaminated by the corresponding selenium compound.

The details of the experiments reported here will be published elsewhere.

H. DAM, G. KOFOED NIELSEN,
INGE PRANGE, and E. SØNDERGAARD

Department of Biochemistry and Nutrition, Polytechnic Institute, Copenhagen, July 12, 1957.

Zusammenfassung

Die exsudative Diathese, welche bei Küken durch Verfütterung einer Vitamin-E-freien Nahrung mit Torulahefe als Proteinquelle hervorgerufen wird, wird mit dem nicht unbeträchtlichen Gehalt dieser Hefe an leicht oxydierbaren Fettsäuren in Verbindung gesetzt.

Die Vitamin-E-freie Torula-Hefe-Nahrung führt zu Peroxydation des Körperfettes, wie es früher in entsprechenden Versuchen mit Kasein-Lebertran-Nahrungen gefunden wurde.

Die von amerikanischen Forschern gefundene Schutzwirkung von Selen gegen exsudative Diathese wird bestätigt.

Das Auftreten von Encephalomalacie wurde durch Selen nicht verhindert.

⁹ H. DAM, I. KRUSE, INGE PRANGE, and E. SØNDERGAARD, *Biochim. biophys. Acta* 2, 501 (1948).

Prophylactic Effect of Selenium Dioxide against Degeneration (White Striation) of Muscles in Chicks

It is known (DAM, PRANGE, and SØNDERGAARD¹) that chicks reared on vitamin E-deficient, low-casein diets, with or without added fat, develop degeneration of muscles within 5 weeks. Macroscopically this form of degeneration appears as a white striation along the muscle fibers. The condition is prevented by vitamin E, and counteracted, to a large extent, by adding cystine (DAM, PRANGE, and SØNDERGAARD¹) or methionine (MACHLIN and SHALKOP²) to the diet.

¹ H. DAM, INGE PRANGE, and E. SØNDERGAARD, *Acta pathol. microbiol. scand.* 31, 172 (1952).

² L. J. MACHLIN and W. T. SHALKOP, *J. Nutr.* 60, 87 (1956).

After having been notified by personal communications from Dr. E. L. R. STOKSTAD of The American Cyanamid Company, Research Division, and Dr. K. SCHWARZ, National Institutes of Health, Bethesda, Md., of the protective effect of selenium against exudative diathesis in chicks, a finding which we have confirmed (DAM, KOFOED NIELSEN, PRANGE, and SØNDERGAARD³), we have tested the effect of selenium dioxide against the type of muscular degeneration mentioned above.

Two groups of ten day-old chicks were used for the experiment. After twelve days on a commercial diet (DAM, HARTMANN, JACOBSEN, and SØNDERGAARD⁴), one group was shifted to the basal diet indicated in the Table, and the other to the same basal diet plus 7 parts per million of SeO_2 (5 p.p.m. of Se). One chick in the selenium group died accidentally after a few days.

The other chicks in both groups were sacrificed by decapitation after having received the experimental diets for five weeks, and autopsied.

Basal Diet	%
Crude casein	15
Gelatin	3
Salt mixture (DAM and SØNDERGAARD ⁴) . .	5.17
Vitamin mixture (DAM and SØNDERGAARD ⁴)	0.1
Choline chloride	0.2
Sucrose	76.53
	100.00

+ 0.001 g dicalciumsalt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester (Synkavit 'Roche') per 100 g diet. Vitamins A and D₃ were given in aqueous solution (DAM, HARTMANN, JACOBSEN, and SØNDERGAARD⁴) 0.1 ml twice a week.

The average weights of the chicks in the two groups were 80 and 81 g at the beginning and 275 and 252 g (the selenium group) at the end of the experiment.

Seven out of the ten chicks in the unsupplemented group had white striation of breast muscles, whereas in the group receiving the SeO_2 supplement only one out of the nine surviving showed this symptom.

The result obtained by adding 7 p.p.m. of SeO_2 to the diet was approximately the same as previously found by adding 0.5% of cystine (DAM, PRANGE, and SØNDERGAARD¹).

H. DAM and E. SØNDERGAARD

Department of Biochemistry and Nutrition, Polytechnic Institute, Copenhagen, August 3, 1957.

Zusammenfassung

Zwei Gruppen von je 10 Küken wurden während fünf Wochen mit einer künstlichen, Vitamin-E-freien Nahrung von niedrigem Kaseingehalt gefüttert. Die eine Gruppe erhielt eine Zulage von 7 mg Selendioxyd per kg Nahrung. Sieben Küken in der unsupplementierten Gruppe zeigten makroskopische Muskelveränderungen, während bei den Küken, welche die Selendioxydzulage erhielten, nur eines dieses Symptom aufwies.

³ H. DAM, G. KOFOED NIELSEN, INGE PRANGE, and E. SØNDERGAARD, *Exper.* 13, 493 (1957).

⁴ H. DAM, S. HARTMANN, J. E. JACOBSEN, and E. SØNDERGAARD, *Acta physiol. scand.* (1957) (in press).

⁵ H. DAM and E. SØNDERGAARD, *Acta pharm. tox. Kbh.* 9, 131 (1953).

Collagen in Experimental Lathyrism¹

Since lathyrism has been known mainly from the morphological aspect, we wish to report here the effect of sweet pea diet on the synthesis of collagen in growing rats. MIELKE, LALICH, and ANGEVINE² found recently, that the administration of the toxic agent (β -amino-propionitrile) decreased the synthesis of hydroxyproline in croton oil pouches. The findings reported below agree well with their results.

The experimental diet³ contained 56% sweet peas and the control diet ordinary peas respectively. The rats (Wistar stock, both males and females) were fed with diet *ad libitum* in individual cages. The weanling animals weighed in the beginning 40 g (mean) and after 2 months in the control group 135 g (mean) and in the lathyrus group 100 g (mean).

Wounds of about 1 cm length were cut (in local anaesthesia) in the backs of the animals and closed with continuous silk suture. No infections occurred. After five days the animals were killed. Strips (1 cm broad), containing the scar transversely in the middle, were cut from the skins and the tensile strength up to the rupture was measured with a simple system of hanging weights. In the control group (5 rats), the tensile strength of the scars was on the average 140 g (range 106–181 g) and in lathyrus-group (4 rats) 57 g (33–87 g). The thickness of the corium was 0.25 mm (mean) in the control group and in the lathyrus group 0.15 mm (mean).

To check the stability of the collagen, the thermal shrinking point was determined from 4 samples of tail tendon in each group. It was identical and normal in both groups (61°–62°C).

The skin samples were cleaned mechanically from hair and fat, ground and finally extracted with ether and acetone. The amount of hydroxyproline was estimated (after conversion of the collagen to gelatine) according to NEUMANN and LOGAN⁴ and tyrosine according to

HEIDELBERGER and MACPHERSON⁵. The respective bone samples were similarly obtained from the thigh-bones. Bone salts were not removed.

The 'tyrosine'-content differed in bone gelatine between the lathyrus and control groups (means 0.28% and 0.17%, $P < 0.01$). This was not found in skin samples.

The non-collagenous residues contained very little hydroxyproline. There was no differences in the amount of 'tyrosine' in the skin samples, but again in the bone it was higher in the lathyrus than in the control group (means 0.35% and 0.25% respectively, $P < 0.10$). Against this background the decrease in the hydroxyproline in the bones is still more significant.

L. KALLIOMÄKI, MAIJA YLI-POHJA,
and E. KULONEN

Department of Medical Chemistry, University of Turku (Finland), August 5, 1957.

Zusammenfassung

Mit Wickendiät synthetisieren wachsende Ratten weniger Hydroxyprolin als Kontrollen, und die Zugfestigkeit des Narbengewebes ist vermindert. Der Wärmeschrumpfungspunkt des Collagens ist unverändert. In der Haut bleibt die Menge des Gelatin«tyrosins» gleich, während sie im Knochen anscheinend vermehrt ist.

⁵ M. HEIDELBERGER and C. F. M. MACPHERSON, *Science* 97, 405 (1943).

Ein neuer vorteilhafter Substitutionstypus der Lokalanästhetika

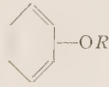
Auf Grund von Erwägungen über die Bedeutung physikalisch-chemischer Eigenschaften für den Wirkungsmechanismus von Arzneimitteln wird bei der rationalen Synthese von Lokalanästhetika oft die Alkoxy-Substitution angewandt. Es soll durch Vergrößerung der Lipoidlöslichkeit die Wirksamkeit erhöht werden. Die geeignetste Länge der Alkoxykette liegt gewöhnlich bei C₂ bis C₄, höhere Derivate sind meist zu stark hydrophob (geringe Wasserlöslichkeit, Hydrolyse der Salze in Wasserlösung).

In Fortsetzung unserer Studien über lokalanästhetisch wirksame basische Ester der alkoxysubstituierten Arylcarbaminsäuren¹ haben wir im Bestreben, lipophile Derivate herzustellen, ohne ihre unvorteilhaften Eigenschaften, eine Reihe von Diäthylaminoäthylestern isomerer Phenoxy-, Benzyloxy- und Phenyläthoxycarb-

¹ A. SEKERA, A. BOROVANSKÝ, I. JAKUBEC, K. PALÁT und Č. VRBA, *Českoslov. farm.* 5, 388 (1956). – K. PALÁT, A. SEKERA und Č. VRBA, *Chem. listy* 51, 563 (1957); *Exper.* 12, 273 (1956).

	Hydroxyproline in % of defatted tissue	
	Skin	Bone
	Mean (range)	Mean (range)
Lathyrus group (5 rats)	7.80 (7.35–8.55)	1.84 (1.50–2.40)
Control group (4 rats)	8.51 (8.05–9.05)	2.31 (1.89–2.43)
P of change occurrence of the difference	< 0.10	< 0.05

Struktur und pharmakologische Wirkung der hergestellten Verbindungen

Präparat Nr.	 $\text{NHCOOCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2 \cdot \text{HCl}$	Schmelzpunkt °C	Berechnet Gefunden		Relative Wirksamkeit bei		LD 50 mg/kg
			% N	% Cl	Ober- flächen- anästhesie	Infiltra- tions- anästhesie	
	$R =$						
S 50	2-C ₆ H ₅	174,5	7,68 7,84	9,72 9,87	4,5	9,3	270
S 51	3-C ₆ H ₅	132	7,68 7,49	9,72 9,76	7,8	19,6	500
S 52	4-C ₆ H ₅	136–137	7,68 7,60	9,72 9,77	11,5	24	660
S 53	2-C ₆ H ₅ CH ₂	104–105	7,39 7,47	9,36 9,34	14,3	33	235
S 54	3-C ₆ H ₅ CH ₂	127–128	7,39 7,36	9,36 9,27	9,2	14,7	600
S 55	4-C ₆ H ₅ CH ₂	130–131	7,39 7,36	9,36 9,63	3,2	3,7	500
S 56 *	2-C ₆ H ₅ CH ₂ CH ₂	—	—	—	16,7	24	170
S 57	3-C ₆ H ₅ CH ₂ CH ₂	119	7,13 7,31	9,02 8,95	37	38,5	210
S 58	4-C ₆ H ₅ CH ₂ CH ₂	152	7,13 7,02	9,02 9,04	7,1	7,4	770
Cocain					1	3,6	125
Procain					0,15	1	630

* Die Substanz wurde nur in Form der flüssigen Base hergestellt und gereinigt (n_D^{25} : 1,5446).

Für C₂₁H₂₈O₃N₂ (356,5) berechnet: 70,76% C, 7,92% H, 7,86% N,
gefunden: 70,94% C, 7,85% H, 7,94% N.

anilsäuren synthetisiert. Die Strukturen der Substanzen sind aus der Tabelle ersichtlich.

Die Verbindungen wurden auf die übliche Weise² durch Reaktion entsprechender aromatischer Amine mit Phosgen und darauffolgende Überführung der entstandenen aromatischen Isocyanate mit Diäthylaminoäthanol in die betreffenden basischen Ester hergestellt. Die hierzu benötigten aromatischen Amine wurden durch katalytische Reduktion der entsprechenden Nitroderivate gewonnen, teils durch Reaktion der Phenolate mit Nitrophenylhalogeniden, teils durch Reaktion von Nitrophenolaten mit Alkylhalogeniden. Die Endprodukte wurden in Form von Hydrochloriden dargestellt, mit Ausnahme des S 56, dessen Salz nicht in kristalliner Form erhalten werden konnte und darum als Base isoliert und gereinigt wurde. Die Hydrochloridlösung erhielten wir in diesem Fall durch Auflösen der Base in äquivalenter Menge verdünnter HCl.

Von allen basischen Estern prüften wir die Wirksamkeit bei Oberflächen- und Infiltrationsanästhesie und die Toxizität. Die Wirksamkeit bei Oberflächenanästhesie (Kaninchenhornhaut, Standard Cocain *M*/100) und Infiltrationsanästhesie (Meerschweinchen, intradermal, Standard Procain *M*/50) konnte durch Ermitteln und Vergleichen gleichwirksamer molarer Konzentrationen der getesteten Substanzen mit konstanten Konzentrationen der Standarde festgestellt werden³. Die Toxizität wurde nach KÄRBER⁴ durch Bestimmung der LD 50 an weissen Mäusen des H-Stammes nach subkutaner Verabreichung ermittelt.

Aus den Ergebnissen der pharmakologischen Prüfungen (Tabelle) ist ersichtlich, dass die hergestellten Substanzen bei relativ geringer Toxizität sowohl bei Oberflächen- als auch bei Infiltrationsanästhesie allgemein sehr wirksam sind. Als bestes Präparat erwies sich der *m*-Phenyläthoxycarbanilsäure-diäthylaminoäthylester (S 57), welcher nahezu 40mal wirksamer als Kokain bei Oberflächenanästhesie wie auch als Procain bei Infiltrationsanästhesie ist. Betrachtet man neben der Wirksamkeit auch die Toxizität der untersuchten Präparate, so zeigt den vorteilhaftesten therapeutischen Index der *p*-Phenoxycarbanilsäure-diäthylaminoäthylester (S 52), welcher bei Oberflächenanästhesie 11mal wirksamer als Kokain und bei Infiltrationsanästhesie 24mal wirksamer als Procain ist. Seine Toxizität ist dabei wie diejenige von Procain und etwas weniger als ein Fünftel der Toxizität des Kokains. Auf Grund von Versuchsergebnissen über die örtliche Verträglichkeit können einige Präparate zur klinischen Prüfung besonders für Oberflächenanästhesie empfohlen werden. Ausführliche experimentelle Ergebnisse des chemischen und pharmakologischen Teiles werden an anderer Stelle veröffentlicht.

J. SOVA, A. SEKERA und Č. VRBA

Institut für pharmazeutische Chemie der Masaryk-Universität und Pharmakologisches Institut der Fakultät für Veterinärmedizin, Brno (Tschechoslowakei), 25. Juni 1957.

Summary

Highly active and relatively little toxic local anaesthetics from the group of aroxy- and aralkoxycarbanilic acids were developed. The substances were tested for local anaesthetic activity in surface and infiltration anaesthesia.

² A. SEKERA, A. BOROVANSKÝ, I. JAKUBEC, K. PALÁT und Č. VRBA, českoslov. farm. 5, 388 (1956). – A. SEKERA, I. JAKUBEC, J. KRÁL und Č. VRBA, Chem. listy 46, 762 (1952).

³ Č. VRBA und A. SEKERA, Arch. intern. Pharmacod. (im Druck).

⁴ G. KÄRBER in J. H. BURN, Biologische Auswertungsmethoden (Berlin 1937), S. 29.

Nicotinamide in Adenocarcinoma 755 and in the Milk of Mice Carrying the 'Agent' of Spontaneous Mammary Tumor

The presence of pyridine nucleotides and of nicotinamide in a variety of normal tissues and in certain neoplastic growths, either of spontaneous origin or resulting from implants in laboratory animals, has been described in the literature¹. This is a brief report of the identification of nicotinamide in implanted mammary adenocarcinoma 755 in C57Bl mice and in the milk of Paris RIII mice with mammary carcinoma acquired in infancy through the nursing influence referred to as the 'milk agent'. Identification was made by means of (1) R_f values, (2) light-absorption curves and (3) conversion to nicotinic acid. In the course of this work a previously unreported color reaction of nicotinamide with ninhydrin was observed and will be described.

The tumors were dropped into liquid nitrogen immediately on removal from the ether-killed mice, disintegrated and dried from the frozen state. The dried tissue was treated exhaustively with ether and the extract stirred vigorously with acidified water. The last step was repeated. The combined water solutions were concentrated under reduced pressure and used for paper chromatographic analysis. Despite precautions it is possible that some of the nicotinamide was derived from splitting of pyridine nucleotides.

R_f Values. Four solvent systems were used. (1) 60 ml *n*-butanol and 10 ml 0.7 *M* NH_4OH ; (2) 77 ml *n*-butanol, 10 ml formic acid and 13 ml water; (3) 72% phenol and (4) 40 ml *n*-butanol, 10 ml acetic acid and 10 ml water. The R_f values were 0.64, 0.41, 0.92 and 0.64, respectively. They were the same, within 5%, for sample of known nicotinamide.

Light-Absorption. To free it of possible contamination before making measurements the compound was eluted from the chromatogram with *N*/100 HCl, the solution concentrated under reduced pressure and respotted using a different solvent system. The eluted compound from the second chromatogram had the same ultraviolet light-absorption curves in *N*/100 HCl and at pH 9 as those of corresponding solutions of known nicotinamide similarly processed².

Conversion to Nicotinic Acid. When the eluates from chromatograms of tumor extracts were evaporated to dryness and the residues taken up in a small volume of *N*/1 HCl and heated for 2 h at 100° the nicotinamide was converted to nicotinic acid. Using solvent systems 1, 2 and 4 the R_f values of the product were 0.18, 0.17 and 0.22; they were the same for acid-treated, known nicotinamide. Also the ultraviolet light-absorption curves in *N*/100 HCl and at pH 9 of the eluted product were the same as those of the corresponding solutions of eluted, known nicotinic acid³.

Nicotinamide was similarly extracted from the kidneys, livers and spleens of the tumor-bearing mice.

Reaction with Ninhydrin. The tissue-extracted compound gave a pale-rose color similar to that obtained with

very small amounts of glycine when paper chromatograms on which it was present were sprayed with a solution of ninhydrin (0.1% in absolute ethanol). An authentic sample of nicotinamide gave the same color; the intensity resulting from 40 γ was about equal to that given by 4 γ of glycine.

Mouse Milk. The fat-free milk was dried from the frozen state and then treated as was the tumor tissue. A chromatogram showed the presence of a compound having the same ultraviolet light-absorption curve as that of nicotinamide and responding to the above-described color test with ninhydrin; its R_f value, however, was 0.14 (solvent 2). Evaporation of a solution in *N*/100 HCl with mild heating gave a compound with R_f values of 0.64 and 0.41 (solvents 1 and 2) which are the same as those of the tumor-extracted compound and of known nicotinamide. This compound also had the typical nicotinamide absorption curve in the ultraviolet and formed nicotinic acid when heated with *N*/1 HCl at 100°.

V. Ross

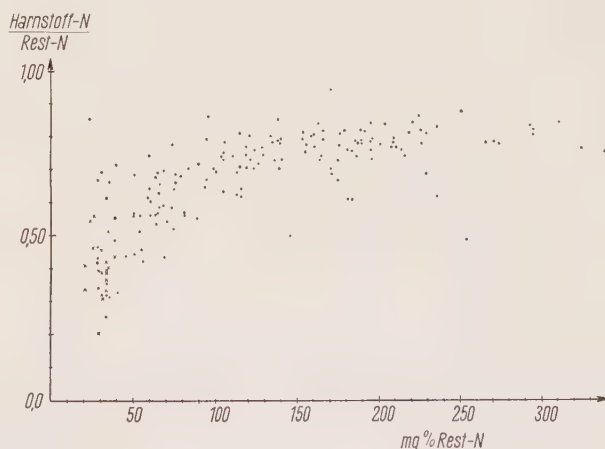
Department of Biochemistry, College of Physicians and Surgeons, Columbia University and Francis Delafield Hospital, New York City, April 23, 1957.

Résumé

L'auteur montre que la nicotinamide se trouve dans l'adénocarcinome 755 et aussi, sous forme d'un dérivé non-identifié, dans le lait de souris porteuses du «milk agent». Il décrit en outre une réaction colorée de la nicotinamide avec la ninhydrine.

Das Verhalten des Quotienten Harnstoff-N:Rest-N bei normalen und nephrektomierten, urämischen Ratten

Der Quotient Harnstoff-N:Rest-N beträgt bei 22 leber-, herz- und nierengesunden Menschen 0,39. 156 Bestimmungen bei 36 nierenkranken Patienten mit N-Re-



Harnstoff-N/Rest-N bei 36 Nierenpatienten (•) und 22 herz-, leber- und nierengesunden Kontrollpersonen (×)

¹ F. BERNHEIM and A. V. FELSOVANYI, *Science* **81**, 76 (1940). – H. v. EULER, F. SCHLENK, H. HEIWINKEL, and B. HÖGBERG, *Z. physiol. Chem.* **256**, 208 (1938). – C. CARRUTHERS and V. SUNTZEFF, *Arch. Biochem. Biophys.* **45**, 140 (1953); *J. Cancer Res.* **12**, 879 (1952). – B. CHANCE, *Trans. N. Y. Acad. Sci.* **16**, 74 (1953).

² H. H. G. JELLINEK and M. G. WAYNE, *J. phys. Chem.* **55**, 173 (1951).

³ R. F. EVANS, E. F. G. HERINGTON, and W. KYNASTON, *Trans. Faraday Soc.* **49**, 1284 (1953).

tention ergaben einen Quotienten von 0,69 im Durchschnitt (Abb. 1). Theoretisch kann die Erhöhung des Harnstoff-N-Anteils am Rest-N hepatogen oder nephrogen sein.

Tabelle I

Rest-N und Harnstoff-N im Plasma normaler und nephrektomierter Ratten

Versuch Nr.	Normale Ratten		Nephrektomierte Ratten	
	Rest-N mg%	Harnstoff-N mg%	Rest-N mg%	Harnstoff-N mg%
1	34	8	290	228
2	41	13	146	101
3	44	14	216	153
4	56	28	198	141
5	38	15	218	165
6	44	18	311	268
7	36	9	204	154
8	38	10	309	247
9	42	13	234	164
10	42	14	380	221
11	45	11	220	168
12	55	20	300	232
13	35	18	220	156
14	45	13	256	197
15	49	17	275	216
16	47	13	296	215
17	54	16	201	151
18	48	16	279	223
19	48	17	175	120
20	14	12	275	211
21	51	18	186	133
22	39	12	281	212
23	53	16	284	214
24	45	12	329	261
	M=43,5	M=14,7	M=253,5	M=189,6
Harnstoff-N Rest-N	0,33		0,74	

Tabelle II

Desaminierungsfähigkeit und Harnstoffbildung überlebender Leberschnitte von normalen und nephrektomierten, urämischen Ratten; Substrat D,L-Alanin

Versuch Nr.	γ NH ₃ -N/mg/h			Q _{Hst} (mm ³ CO ₂ /mg/h)	
	Normale Ratten	Nephrektomierte Ratten	Differenz II-I	Normale Ratten	Nephrektomierte Ratten
1	1,04	4,76	3,72	7,75	6,09
2	0,80	0,14	- 0,66	2,87	4,12
3	0,40	0,84	0,44	6,95	8,02
4	3,19	2,80	- 0,39	10,64	11,56
5	1,87	2,60	0,73	4,13	6,43
7	0,49	3,53	3,04	4,19	8,59
8	1,19	2,29	1,10	5,89	3,68
9	0,59	2,44	1,85	8,91	6,59
10	0,89	2,28	1,39	5,10	4,30
11	0,67	1,19	0,52	5,13	6,88
12	0,43	2,39	1,96	4,73	5,82
13	0,61	2,76	2,15	5,85	5,19
14	3,05	3,24	0,19	9,23	7,28
15	0,85	1,73	0,88	7,77	8,54
16	2,51	3,88	1,37	5,18	8,13
17	1,79	2,07	0,28	4,95	5,87
18	1,34	4,73	3,39	10,10	10,52
19	5,47	5,27	- 0,20	6,36	7,33
21	1,01	2,38	1,37	7,15	8,78
22	1,42	2,50	1,08	6,86	8,67
23	0,61	5,43	4,82	5,64	9,70
24	1,55	2,56	1,01	8,00	6,77
25	4,39	3,65	- 0,74	15,70	11,81
	M _I = 1,57 σ _I = $\pm$ 1,33	M _{II} = 2,85 σ _{II} = $\pm$ 1,34		M _I = 6,9	M _{II} = 7,4
	Der Unterschied von M _I und M _{II} ist signifikant ($p < 0,01$).				

1. Von der Leberfunktion sind abhängig: a) Vermehrte Desaminierung und Transaminierung retinierter Substanzen und nachfolgend b) vermehrte Harnstoffbildung.

2. Von der Nierenfunktion sind abhängig: I. a) Verminderte Harnstofffiltration; b) vermehrte tubuläre Harnstoffrückdiffusion; II. a) verminderte Filtration der Residual-N-Substanzen (Rest-N minus Harnstoff-N); b) verminderte tubuläre Rückresorption der Residual-N-Substanzen.

Um die Frage zu entscheiden, ob die Erhöhung des Quotienten Harnstoff-N: Rest-N auf Leber- oder Nierenfunktionsstörungen zurückzuführen sei, wurden Quotienten normaler Ratten mit solchen nephrektomierter, urämischer Tiere verglichen. Ferner wurden an Leberschnitten dieser Tiere Desaminierungsfähigkeit und Harnstoffbildung untersucht.

Methodik

1. Bestimmung von Rest-N (KJELDAHL) und Harnstoff (CONWAY) im Plasma von 24 Ratten 2-4 Tage nach Nephrektomie und 24 Kontrolltieren.

2. Harnstoff-Synthese überlebender Leberschnitte aus Ammoniak und Kohlensäure¹ (24 Ratten 2-4 Tage nach Nephrektomie und 24 Kontrolltiere):

a) Inkubationslösung: 4,48 ml Krebs-Ringerlösung, 0,31 ml 1% Ammoniumchloridlösung, 0,1 ml 5% Brenztraubensäurelösung, 0,11 ml 0,9% Ornithinlösung. Sätti-

¹ H. A. KREBS und K. HENSELEIT, Hoppe-Seylers Z. 210, 33 (1932).

gung der Lösung mit Gasgemisch von 95% Sauerstoff und 5% Kohlensäure.

b) Inkubationsdauer 2 h bei 37,5°C.

c) Harnstoffbildung wurde gemessen durch den Quotienten $Q_{Hst} = \text{mm}^3 \text{ CO}_2/\text{mg Trockengewicht/h}$ ($22,4 \text{ mm}^3 \text{ CO}_2 = 60 \gamma$ Harnstoff). Im Hauptraum des Warburg-Gefäßes 1,9 ml Inkubationslösung und 0,3 ml Acetatpuffer², im Anhang des Gefäßes 0,3 ml Urease-lösung³. Versuchsdauer 30 min, Ablesen 5, 10, 20 und 30 min nach Erreichen der Druckkonstanz im Thermo-barometer. Wägen der Gewebsschnitte 2 h nach Trocknen bei 105°C.

3. Desaminierungsfähigkeit und Harnstoffbildung überlebender Leberschnitte mit D,L-Alanin als Substrat. Bestimmung von Ammoniak⁴ und Harnstoff (siehe Methodik 2c) in der Inkubationslösung.

Resultate

1. Der Quotient Harnstoff-N: Rest-N betrug bei urämischen Ratten 0,74, bei Kontrollen 0,33 (Tab. I).

2. Die Harnstoffbildung aus Ammoniak und Kohlensäure in der Leber normaler und nephrektomierter Ratten zeigte keine Unterschiede.

² 27,2 g Natriumazetat ($\text{CH}_3\text{COONa} \cdot 3 \text{ H}_2\text{O}$) mit 6 g Eisessig versetzt und mit Aq. dest. ad 100 ml aufgefüllt, pH 5,0.

³ 500 mg Jack-Bohnen-Urease (Paul Lewis Lab., Milwaukee, Wis.) in 5 ml Aq. dest. gelöst.

⁴ E. J. CONWAY, Biochem. J. 29, 2755 (1935).

3. Die aus D,L-Alanin entstandene Harnstoffmenge war in beiden Gruppen gleich. Intermediär kam es bei urämischen Ratten zu einer signifikanten Steigerung der Ammoniakbildung durch Leberschnitte im Vergleich zu Kontrollen (Tab. II).

Diskussion

1. Bei nephrektomierten, urämischen Ratten wurden zwei wesentliche Befunde erhoben: a) signifikante Erhöhung des Quotienten Harnstoff-N:Rest-N, b) signifikante Steigerung der intermediären Ammoniakbildung (Harnstoffsynthese aus D,L-Alanin). Diese Befunde sprechen für gesteigerte Desaminierungs- und Transaminierungsvorgänge in der Leber von Ratten mit Stickstoff-Retention.

2. Die Harnstoffbildung aus Ammoniak und Kohlensäure und aus D,L-Alanin ergab keine Unterschiede zwischen beiden Gruppen. Dies kann folgendermassen erklärt werden: Das citrullinbildende Fermentsystem (1. Stufe der Harnstoffbildung) in den Mitochondrien der Leberzellen ist unter anderem abhängig von der Adenosintriphosphorsäure. Da diese Phosphorverbindung sehr labil ist, muss sie ständig resynthetisiert werden. Die Resynthese der Adenosintriphosphorsäure ist an das Vorhandensein von Glutaminsäure gekoppelt⁶. Glutaminsäure entsteht in Leberschnitten bei Gegenwart von Ammoniumsalzen⁷. Möglicherweise war die Menge der *in situ* gebildeten Glutaminsäure zu gering, um die Adenosintriphosphorsäurebildung zu gewährleisten. Zusatz von Glutaminsäure zur Inkubationsflüssigkeit hätte die Adenosintriphosphorsäuresynthese nicht beschleunigt, da die Glutaminsäure sehr langsam in intakte Gewebszellen diffundiert⁷.

3. Die gesteigerten Desaminierungs- und Transaminierungsvorgänge bei urämischen Ratten führen zu vermehrter Harnstoffbildung. Die Ursache der gesteigerten Harnstoffsynthese ist wahrscheinlich in der Entgiftung toxischer Amine zu suchen. Verminderte Desaminierung und Transaminierung bedingen Residual-N-Erhöhung. Untersuchungen urämischer Patienten weisen auf einen möglichen Zusammenhang zwischen Residual-N-Erhöhung und Auftreten von Bewusstseinsstörungen hin⁸. In solchen Fällen werden wahrscheinlich die betreffenden Fermentsysteme in der Leber durch Störungen im Säuren-Basengleichgewicht, im Elektrolytstoffwechsel und in der Sauerstoffversorgung der Leber (Anämie) gehemmt.

Wir danken dem Schweizerischen Nationalfonds für die Unterstützung der Arbeit.

R. BOSSHARDT, H. THÖLEN und
F. ENDERLIN

Medizinische Universitätsklinik, Basel, 1. Oktober 1957.

Summary

(1) The quotient urea nitrogen:non-protein nitrogen was determined in nephrectomized uremic rats and compared with the quotient in control animals. The quotient in nephrectomized uremic animals was 0.74,

⁵ Z. STARY in *Physiologische Chemie* von B. FLASCHENTRÄGER und E. LEHNARTZ, II/2/a (Berlin, Göttingen, Heidelberg 1956).

⁶ H. FAHLÄNDER, P. FAVARGER und F. LEUTHARDT, *Helv. chim. Acta* 31, 942 (1948).

⁷ F. LEUTHARDT, H. FAHLÄNDER und H. NIELSEN, *Helv. phys. Acta* 5, 282 (1947).

⁸ H. CHABANIER und A. DE CASTRO GALHARDO, *C. R. Soc. Biol.* 83, 723 (1920). – W. FREY, *Hdb. inn. Med.* VIII (Springer-Verlag, Berlin 1951). – H. THÖLEN und R. BOSSHARDT (im Druck).

in control animals 0.35. The elevation of the quotient is of hepatic origin.

(2) The desamination was increased in the liver of nephrectomized uremic animals in comparison to controls; the urea production was unchanged.

Influence of *in vitro* Added Thyroxin upon the Glucose Uptake of the Rat Diaphragm

The influence of thyroxin (added to the medium) upon isolated organs has been investigated by a great number of authors¹.

The conclusions are entirely controversial; positive and negative results have been reported to about the same extent. The experiment which is principally used, of the influence of added thyroxin upon the oxygen consumption of liver slices gave almost negative results. But, this might be due to the destruction of the thyroxin in the liver which is notoriously very active. Thus we preferred to use muscle tissue in our experiments.

Method.—The diaphragm was taken under deep chloroform anaesthesia from female rats of 150 to 200 g. It was placed into ice-cooled KREBS-HENSELEIT saline added with 1.5% of glucose. The muscle was dissected free from the tendinous center and divided into 7 parts of about 30 mg.

The apparatus of KREBS and HENSELEIT² was used for incubation. The 8 flasks of the apparatus were provided with 0.5 ml of the glucosed saline mentioned above. They were stoppered and weighed. Flask No. 1 was kept for control; the diaphragm fragments were blotted, placed into flasks No. 2–8, stoppered and weighed again.

The flasks were mounted upon the apparatus; the whole was filled with a mixture of 95% O₂ and 5% CO₂ and incubated for 1 h in a stirred water bath at 39°C. The remaining glucose was determined with the method of HAGEDORN and JENSEN. Results were recalculated for 1 g of tissue.

Thyroxin was dissolved in 0.01 NaOH at 2 mg/ml. The further dilutions were carried out with glucosed saline. For the determinations of the influence upon the glucose uptake, it was added to flasks No. 3–8 at concentrations from 10⁻¹⁰ to 10⁻⁵.

Flask No. 2 was kept without thyroxin for control.

Results.—The method was used prior to us by many authors for different experimental purposes. It is generally admitted that there are large differences of the glucose uptake from one animal to another, but that several determinations upon different fragments of the same diaphragm give valid average values. To this we agree; our preliminary determinations gave the following results (see Table I).

For the influence of the thyroxin see Table II.

It can be seen that the glucose uptake rate is increased under the influence of thyroxin. This was observed constantly if thyroxin was added at the concentration of 10⁻⁷ or 10⁻⁶. The inconstancy of the results obtained with a concentration of 10⁻⁵ may be understood, since this concentration is very near to the saturation limit of thyroxin in KREBS-HENSELEIT's saline.

¹ For references see J. COMSA, *Les antithyroïdiens biologiques* (Doine édité., Paris 1953).

² H. A. KREBS and D. HENSELEIT, *K. Schr. physiol. Chem.* 212, 33 (1932).

Table I

Diaphragm No.	Glucose uptake (mg per g/h)
1	5.15 ± 0.32 (standard deviation)
2	4.30 ± 0.34
3	3.85 ± 0.15
4	3.75 ± 0.28
5	1.63 ± 0.05

For a different experimental purpose, 30 similar determinations were performed with the single thyroxin concentration of 10^{-7} . Without exception, the increase of the glucose uptake was observed in all cases.

The uptake rate of the thyroxin-treated preparations was of 179% to 310% of the uptake rate of the control preparations.

Table II

Glucose uptake rate of the rat diaphragm in KREBS-HENSELEIT saline glucosed at 1.5% and added with thyroxin

Thyroxin concentration	Glucose uptake (mg/g/h)			
	Diaphragm No.			
	1	2	3	4
0	2.85	2.28	2.43	3.55
10^{-5}	5.56	7.00	3.02	6.15
10^{-6}	6.06	5.00	5.00	8.15
10^{-7}	5.44	4.20	4.70	7.83
10^{-8}	3.33	2.50	4.50	4.40
10^{-9}	2.91	2.30	3.00	3.70
10^{-10}	2.85	2.25	2.54	3.40

Thus, it could be concluded that thyroxin constantly increased the glucose uptake rate of the rat diaphragm, when added to the medium at an adequate concentration.

J. COMSA

Medical School of the Saarland University, Department of Experimental Medicine and Surgery, Homburg, June 4, 1957.

Résumé

1° La consommation de glucose du diaphragme isolé de rat incubé dans la solution de KREBS-HENSELEIT glucosée est constamment accrue par la thyroxine ajoutée au milieu.

2° La concentration optima pour ces déterminations était de 10^{-7} à 10^{-6} de thyroxine.

Thrombozytose und Eosinophilie bei adrenalektomierten Ratten nach einmaliger 5-Hydroxytryptamininjektion

In früheren Versuchen wurde festgestellt, dass eine einmalige hohe Dosis von 5-Hydroxytryptamin bei Ratten eine Thrombozytose und gleichzeitig eine Eosinopenie hervorruft (STEINER und HEDINGER)¹. Dabei

¹ F. A. STEINER und CHR. HEDINGER, Exper. 12, 109 (1956).

war aber die Möglichkeit nicht auszuschliessen, dass die gefundenen Zellverschiebungen ganz oder teilweise auf einer unspezifischen Serotoninwirkung im Sinne einer Alarmreaktion beruhen könnten. Wir haben deshalb in den vorliegenden Untersuchungen das Verhalten der Thrombozyten und Eosinophilen im peripheren Blut nach einer einmaligen Dosis von Hydroxytryptamin auch bei nebennierenlosen Ratten geprüft.

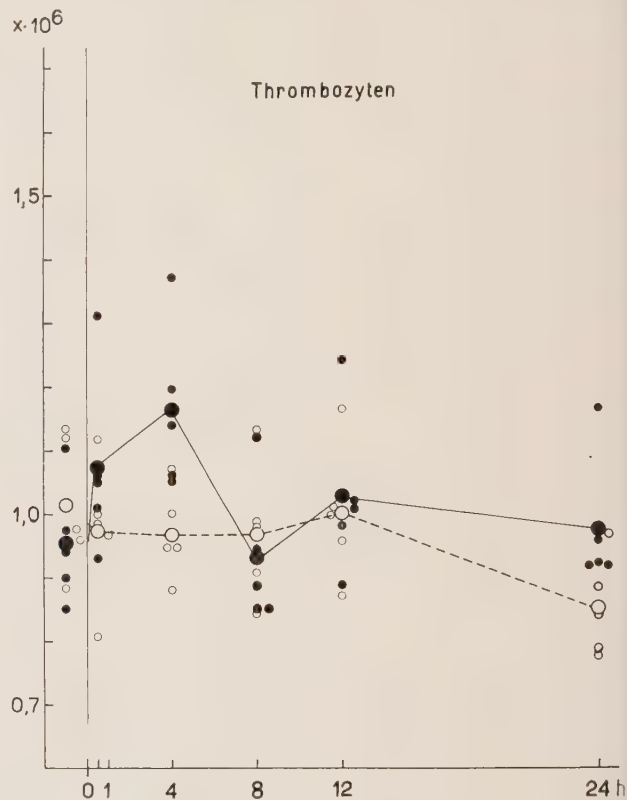


Abb. 1. Thrombozytose im peripheren Blut von Ratten mit intakten Nebennieren nach einmaliger Injektion von 5-Hydroxytryptamin ($80 \mu\text{Mol/kg}$ Körpergewicht).

Abzisse: Bestimmungszeiten unmittelbar vor und nach der Injektion
Ordinate: Thrombozyten pro mm^3 Blut in Millionen.

● ● Mittelwerte nach 5-Hydroxytryptamininjektion.
○ ○ Mittelwerte nach Injektion von 0,9% NaCl-Lösung.
● Einzelwerte ○ Einzelwerte

Versuchsordnung. Fünfzehn 95–210 g schwere männliche und weibliche Albinoratten aus der lang-jährigen Inzucht des Pathologischen Institutes Zürich wurden einzeltig in Pentothal-Äther-Narkose auf lumbalem Wege transperitoneal beidseitig adrenalektomiert. Die Nebennieren wurden dabei samt der Kapsel mit dem Thermokauter abgetragen. Die Tiere erholten sich auch ohne Hormonbehandlung, aber mit 1prozentiger NaCl-Lösung als Trinkwasser, innerhalb der folgenden 2–3 Tage gut. Als Kontrolltiere dienten fünf gleichartige intakte Ratten, die unter den gleichen Bedingungen gehalten wurden, jedoch gewöhnliches Brunnenwasser als Trinkwasser erhielten. Als Nahrung wurden beiden Gruppen Mischkörner-Biskuits verabreicht.

Vorversuche ergaben, dass nebennierenlose Ratten die früher verwendeten hohen Dosen von $250 \mu\text{Mol/kg}$ Körpergewicht nicht länger als 6–8 Stunden überleben. In den folgenden Versuchen wurde deshalb die Dosis der einmaligen subkutanen 5-Hydroxytryptamininjektion

auf 80 $\mu\text{Mol/kg}$ reduziert². Auch bei dieser niedrigeren Dosis überlebten zwar nicht alle nebennierenlosen Ratten die ganze Versuchsdauer, doch konnten noch bei genügend überlebenden Tieren nach 24 h die Thrombozyten- und Eosinophilenwerte bestimmt werden.

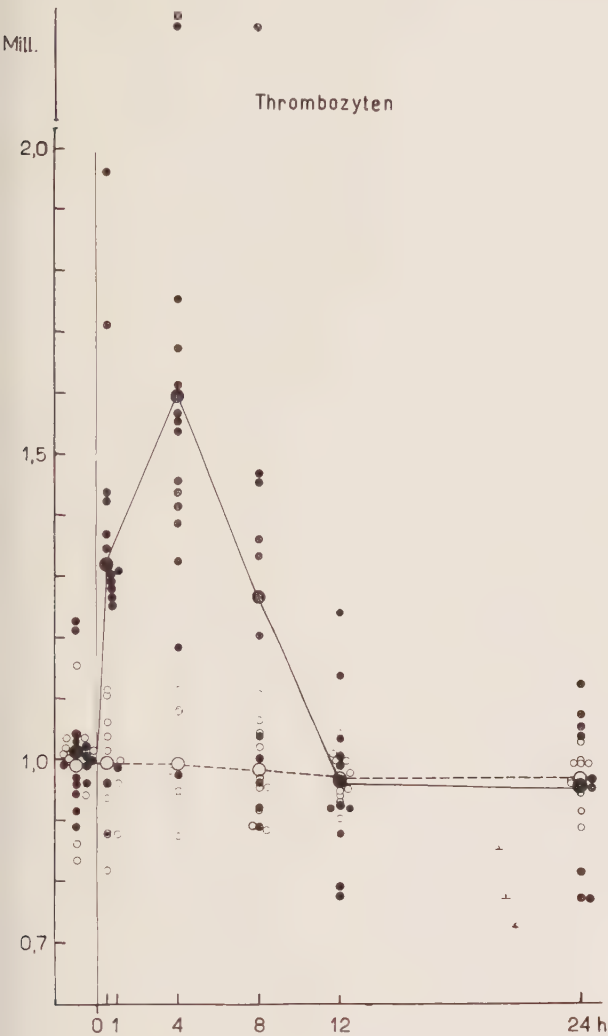


Abb. 2. Thrombozytose im peripheren Blut von nebennierenlosen Ratten nach einmaliger Injektion von 5-Hydroxytryptamin (80 $\mu\text{Mol/kg}$ Körpergewicht).

Abzisse: Bestimmungszeiten unmittelbar vor und nach der Injektion
Ordinate: Thrombozyten pro mm^3 Blut in Millionen.

- Mittelwerte nach 5-Hydroxytryptamininjektion.
- Mittelwerte nach Injektion von 0,9% NaCl-Lösung.
- Einzelwerte ○ Einzelwerte

Bei intakten und nebennierenlosen Tieren wurden die Thrombozyten und eosinophilen Leukozyten im peripheren Blut unmittelbar vor und $\frac{1}{2}$, 4, 8, 12 und 24 h nach subkutaner Injektion von 10 ml/kg 0,9% NaCl-Lösung bestimmt. Am nachfolgenden Tage erhielten die Tiere morgens nüchtern eine subkutane Injektion von 80 $\mu\text{Mol/kg}$ 5-Hydroxytryptaminhydrochlorid in 0,9% NaCl-Lösung. Wiederum wurden die Thrombozyten und eosinophilen Leukozyten unmittelbar vor und $\frac{1}{2}$, 4, 8, 12 und 24 h nach der Injektion bestimmt. Die Zählung

der Thrombozyten erfolgte direkt in der Fuchs-Rosenthal-Kammer mit Hilfe des Phasenkontrastmikroskopes. Die eosinophilen Leukozyten wurden ebenfalls direkt nach der modifizierten Methode von DUNGER bestimmt³. Die Blutentnahme erfolgte aus den Schwanzvenen.

Ergebnisse. Die Thrombozyten steigen bei den intakten Tieren (Abb. 1) auch nach 80 μMol 5-Hydroxytryptamin pro kg Körpergewicht signifikant ($p < 0,05$)⁴ über die Kontrollwerte des Vortages an. Das Maximum der Thrombozytose wird jedoch schon nach 4 h erreicht,

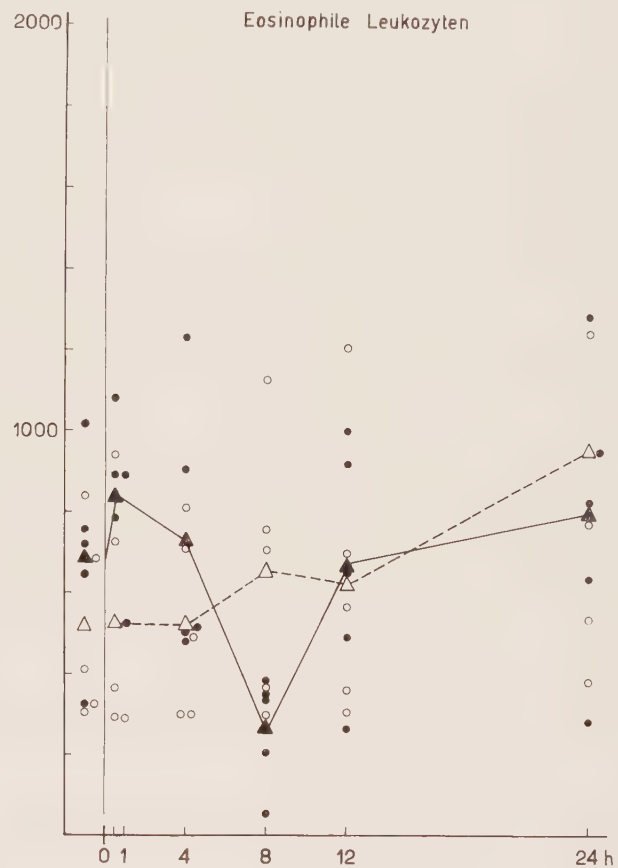


Abb. 3. Abfall der Zahl der eosinophilen Leukozyten im peripheren Blut von Ratten mit intakten Nebennieren nach einmaliger Injektion von 5-Hydroxytryptamin (80 $\mu\text{Mol/kg}$ Körpergewicht).

Abzisse: Bestimmungszeiten unmittelbar vor und nach der Injektion
Ordinate: Eosinophile pro mm^3 Blut.

- ▲—▲— Mittelwerte nach 5-Hydroxytryptamininjektion.
- △—△— Mittelwerte nach Injektion von 0,9% NaCl-Lösung.
- ▲ Einzelwerte △ Einzelwerte

und nach 8 h sind die Thrombozytenwerte wieder normalisiert. Bei den nebennierenlosen Tieren (Abb. 2) ist die Thrombozytose noch ausgeprägter und dauert länger an, indem der $\frac{1}{2}$ - und der 4-h-Wert signifikant ($p < 0,01$)⁴ erhöht sind und der Ausgangswert erst nach 12 h wieder erreicht wird.

Gegenüber unserem früheren Versuche¹ zeigt sich bei der niedrigen Dosierung des 5-Hydroxytryptamins eine entsprechend geringere und kürzer dauernde Thrombozytose nach Serotonin-Injektion. Bei intakten und neben-

² Der Firma Dr. A. Wander AG., Bern, danken wir für das 5-Hydroxytryptaminhydrochlorid.

³ R. SIEBENMANN und C. SANDRI, Klin. Wschr. 34, 706 (1956).

⁴ t -Test nach STUDENT.

nierenlosen Tieren wird das Maximum der Thrombozytose nach 4 h erreicht. Den stärkeren Anstieg der Thrombozyten bei den nebennierenlosen Tieren können wir nicht erklären. Die Versuche zeigen aber deutlich, dass eine Thrombozytose nach 5-Hydroxytryptamininjektionen auch ohne Mitwirkung der Nebennieren zustandekommt.

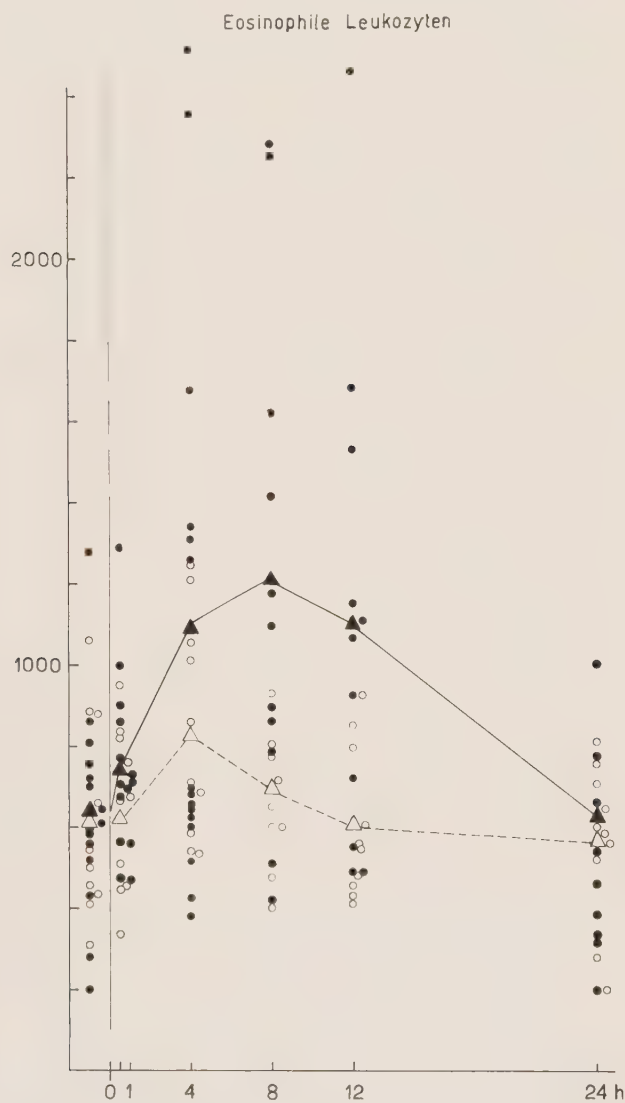


Abb. 4. Anstieg der Zahl der eosinophilen Leukozyten im peripheren Blut von nebennierenlosen Ratten nach einmaliger Injektion von 5-Hydroxytryptamin (80 μ Mol/kg Körpergewicht).

Abszisse: Bestimmungszeiten unmittelbar vor und nach der Injektion
Ordinate: Eosinophile pro mm^3 Blut.

▲ ▲ – Mittelwerte nach 5-Hydroxytryptamininjektion.
– △ – △ – Mittelwerte nach Injektion von 0,9% NaCl-Lösung.
● Einzelwerte ○ Einzelwerte

Die *eosinophilen Leukozyten* fallen bei intakten Ratten (Abb. 3) unter Serotonin, nach einem vorübergehenden geringen Anstieg nach $\frac{1}{2}$ h, nach 8 h signifikant ab ($p < 0,05$)⁴, um nach 12 h wieder den Ausgangswert zu erreichen. Bei den nebennierenlosen Tieren (Abb. 4) bleibt dieser Eosinophilensturz nach 5-Hydroxytryptamin nicht nur aus, sondern es kommt nach 8 und 12 h zu einem signifikanten Anstieg der Eosinophilen ($p < 0,05$)⁴, welche erst nach 24 h den Ausgangs-

wert wieder erreichen. Bei dieser Versuchsgruppe war schon am Vortag nach Injektion von 0,9% NaCl-Lösung eine leichte Eosinophilenvermehrung zu beobachten.

In Übereinstimmung mit unseren früheren Untersuchungsergebnissen führt das Serotonin bei Ratten mit intakten Nebennieren zu einem Abfall der eosinophilen Leukozyten im Blut. Entsprechend der niedrigeren Dosierung ist dieser Abfall von kürzerer Dauer. Die niedrigsten Werte werden auch früher erreicht. Im Gegensatz zur Thrombozytose ist dieser Eosinophilensturz an das Vorhandensein der Nebennieren gebunden. Er bleibt bei der adrenalectomierten Ratte nicht nur aus, sondern wird durch einen deutlichen Anstieg der Zahl der Eosinophilen im peripheren Blut ersetzt.

F. A. STEINER, R. E. SIEBENMANN,
C. SANDRI und CHR. HEDINGER

Pathologisches Institut der Universität Zürich, 4. Juli 1957.

Summary

In adrenalectomized rats, the injection of a single high dose of 5-hydroxytryptamin results, as in intact animals previously reported, in a strong increase of the number of platelets in the peripheral blood. The number of eosinophils, instead of decreasing, also rises. The maxima of increase are not in temporal accordance.

PRO LABORATORIO

Young NH-Mice for the Study of Mitoses in Intact Liver

Since the classical studies of PODWYSZOZKI, most investigators of liver mitosis have studied the regenerating organ¹. Less attention has been paid to mitoses in young mouse liver, since their variability is 'at times so great as to be disconcerting'². As compared to regenerating liver, however, growing mouse liver may be examined in the absence of effects induced by procedures necessary to bring about regeneration. Moreover, by the use of an experimental design which includes provisions for the evaluation of 24-h periodicity³ the variability of mitotic counts can be reduced, in intact, as well as in regenerating⁴ tissues. With the appropriate standardization of environmental conditions⁵, particularly of the lighting regimen⁵, the liver of intact mice of appropriate age may be used for the study of factors affecting mitoses *in vivo*. But in addition to regard for 24-h periodicity⁶, it also seems desirable to employ a stock of mice with a relatively high mitotic count at the peak of daily rhythm. Several stocks of mice were examined in this laboratory from this point of view. The Figure reveals that the NH stock is well suited for studies of mitosis in intact mouse liver.

¹ W. v. PODWYSZOZKI, jr., Beitr. path. Anat. 1, 259 (1886). – M. E. WILSON, R. E. STOWELL, H. O. YOKOYAMA, and K. K. TSUBOI, Cancer Res. 13, 86 (1953).

² J. W. WILSON and E. H. LEDUC, Anat. Rec. 97, 471 (1947).

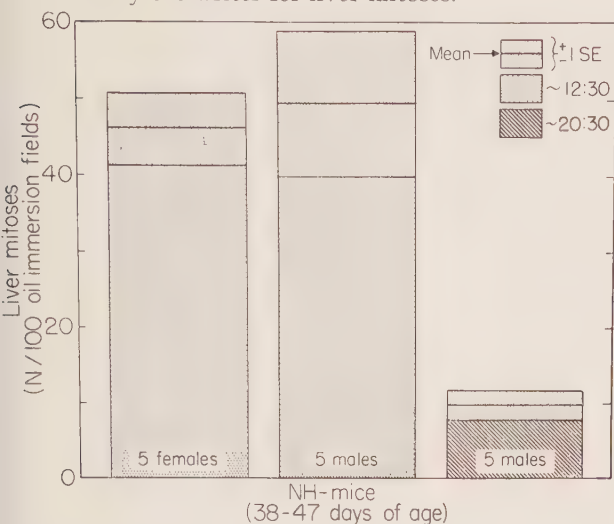
³ F. HALBERG, J. Lancet 73, 20 (1953). – F. HALBERG, H. A. ZANDER, M. W. HOUGLUM, and H. R. MÜHLEMANN, Amer. J. Physiol. 177, 361 (1954).

⁴ C. M. BLUMENFELD, Arch. Path. 36, 493 (1943). J. J. JAFFE, Anat. Rec. 120, 935 (1954).

⁵ F. HALBERG, J. J. BITTNER, and D. SMITH, Z. Vitamin-, Horm. Fermentforsch. (in press).

⁶ C. D. JARDETSKY, C. P. BARNUM, and F. HALBERG, Amer. J. Physiol. 187, 608 (1956).

Of course, the age of the animals examined constitutes a critical factor, since, in keeping with earlier work on many species, mitotic activity was found to decline rapidly during the second month of extrauterine life, in NH-mice as well as in animals of several other stocks, examined by the writer for liver mitoses.



High counts of parenchymal mitoses in young NH liver. Mean mitotic counts on sections of mouse liver (fixed in Bouin's solution, cut at $5\ \mu$, stained with Heidenhain's ironhaematoxylin and eosin). The mice were kept singly housed for 7 days, in a room maintained at $\sim 25.5^\circ\text{C}$, illuminated from 06.00 to 18.00 and darkened from 18.00 to 06.00. Colchicine was not used (cf. MÜHLEMANN *et al.*⁷). Note high counts in mice of both sexes at about the middle of the daily light period. Note also the daynight difference for the males ($= 40.2 \pm 10.3$; $t = 3.91$; $P = 0.005$).

The mean mitotic counts in pinnal epidermis of the male NH-mice, referred to in the Figure were $6.0^{0/00}$ nuclei and $3.6^{0/00}$ nuclei, at 12:30 and 20:30, respectively. From these data, the student of periodicity may infer that the rhythmus of epithelial mitoses in pinnal epidermis and liver parenchyma are not grossly dissociated in their timing along the 24-h scale. By contrast, gross differences in phase characterize the rhythms in liver mitoses on one hand and in certain aspects of hepatic

phospholipid metabolism on the other: a peak in the former occurs at about the trough in the latter⁶. Similar differences in phase characterize the time relations of the mitotic rhythms in liver parenchyma and skin epidermis on one hand and in adrenal parenchyma and stroma on the other hand⁸.

After birth, mitoses in intact mouse liver have been regarded as rare⁹. This conclusion may be expected from studies carried out without experimental provisions made to evaluate the peak of the 24-h mitotic rhythm. Such provisions were made in this laboratory for work on groups of 10 to 20 mice, from each of several inbred stocks and their hybrids (just as for the NH-group of the Figure). The mice were weaned at 3 weeks of age and were studied after a period of standardization of 1 or 2 weeks duration. In such mice, 4 to 5 weeks of age, the nucleus of the parenchymal liver cell is already large⁹ and this circumstance facilitates the recognition of mitoses and the definition of their stages. Variability was of course encountered in all of this work, despite standardization with respect to periodicity, environment, genetics, age and sex. Nonetheless, in each case, the mean count at the peak of rhythm was sufficiently high and the variability restricted to a degree which allowed the economical use of groups of young intact mice for the study of factors affecting hepatic mitoses *in vivo*. So far, however, the line of NH-mice, obtained several years ago from Dr. MARHELLA FRANTZ and maintained by the writer, seems to be particularly well suited for this purpose.

F. HALBERG

Division of Cancer Biology, Department of Pathology, University of Minnesota Medical School, and Cambridge State School and Hospital, Cambridge, Minnesota, August 15, 1957.

Zusammenfassung

Die mittlere Mitosenzahl in der intakten Leber von jungen NH-Mäusen zeigt eine signifikante 24-h-Periodizität. Zur Zeit des täglichen Mitosengipfels ist diese Zahl genügend hoch, so dass sie sich als Kriterium für die Untersuchung der Faktoren eignet, welche die Lebermitosen *in vivo* beeinflussen.

⁸ F. HALBERG, M. J. FRANTZ, and J. J. BITTNER, *Anat. Rec.* (in press).

⁹ M. SISS and H. STEGMANN, *Virchows Arch.* 318, 534 (1950).

Informations - Informationen - Informazioni - Notes

Die Nobelpreise 1957 für Physik, Chemie und Medizin

Die Träger des Nobelpreises für Physik

T. D. Lee und C. N. Yang

sind 1926 bzw. 1928 in China geboren. Sie erhielten ihre wissenschaftliche Ausbildung in Chicago. LEE ist Professor an der Columbia Universität in New York, YANG am Institute for Advanced Study in Princeton, N. J.

Über ihre Entdeckung und deren Folgen wird im nächsten Heft der *Experientia* ein Artikel von Prof. Dr. W. PAULI (ETH, Zürich) mit dem Titel: *Die Verletzung von Spiegelungs-Symmetrien in den Gesetzen der Atomphysik* berichten.

Sir Alexander Robertus Todd

Sir ALEXANDER ROBERTUS TODD, Professor für organische Chemie an der Universität Cambridge, hat in Würdigung seiner Arbeiten über die Nukleotide und Nukleotid-Coenzyme den diesjährigen Nobelpreis für Chemie erhalten. Der Preisträger wurde am 2. Oktober 1907 in Glasgow geboren, studierte von 1928 bis 1934 in Glasgow, Frankfurt und Oxford Chemie, betätigte sich anschliessend in Oxford, Edinburg und London auf dem Gebiete der medizinischen Chemie und erhielt 1937 als Mitarbeiter am Lister Institute of Preventive Medicine einen Lehrauftrag für Biochemie an der Universität London. Bereits 1938 folgte die Chemie-Professur in Manchester, 1944 ein Ruf auf seinen jetzigen Lehrstuhl in Cambridge. Professor TODD hat schon eine Reihe von Auszeichnungen erhalten: 1936 die Meldola-Medaille, 1938 die Lavoisier-Medaille, 1949 die Davy-Medaille

und 1955 die Royal-Medaille; mehrere Hochschulen haben ihm die Würde eines Ehrendoktors verliehen. – Der Beginn der Arbeiten auf dem Nukleotid-Gebiet liegt etwa 15 Jahre zurück: die erste Mitteilung zum Problem der Synthese von Purin-Nukleosiden findet sich im *Journal of the Chemical Society* des Jahres 1943. Rasch wurde es nötig, neue Methoden zu entwickeln. 1945 erschien die erste Arbeit über Phosphorylierungs-Studien. In dasselbe Jahr fällt der Beweis für die Richtigkeit der Lohmannschen Adenosin-triphosphat-Formel. Einer ersten Mitteilung über synthetische Arbeiten auf dem Nukleotid-Gebiet (1947) folgte bald ein erster Bericht über die Synthese des Adenosintriphosphats (1948/49). 1949 waren die Studien über die Konstitution der Nukleoside abgeschlossen, und in das Jahr 1952 fällt der Beginn von Untersuchungen über die Struktur und chemischen Eigenschaften der Nukleinsäuren. Gleichzeitig wandte TODD am Beispiel des Flavin-adenin-dinukleotids seine Aufmerksamkeit erstmals der Synthese der Nukleotid-Coenzyme zu. Der erfolgreichen Synthese der genannten Verbindung folgte die Synthese von Uridin-diphosphat-glukose (1954/56), Uridin-diphosphat-galaktose (1956) und Diphospho-pyridin-nukleotid (1957). Andere Arbeiten, welche TODD bekannt gemacht haben, sind seine Untersuchungen über Haschisch¹ und die Ermittlung der Konstitution von Vitamin B₁₂ (1955).

Professor TODD ist ein hervorragender Organiker, der unter dem Eindruck einer guten biochemischen Schulung sein Können konsequent in den Dienst der Biochemie gestellt hat. Unter dem Titel «The Impact of Chemistry on Biology and Medicine» schreibt er in einem Aufsatz²: «The chemist's position is very neatly put in a remark of the late Sir FREDERICK HOPKINS who said of him 'His may not be the last word in the description of life, but without his help the last word will never be said'». Sir ALEXANDER TODD hat diesen Worten nachgelebt. Der Beitrag, welcher von ihm zur Beschreibung des Lebens geleistet wurde, hat mit der Erteilung des Nobelpreises eine Anerkennung gefunden, der jedermann mit Überzeugung zustimmen wird. M. BRENNER

Daniel Bovet

Le prix Nobel de physiologie et de médecine vient d'être attribué à M. DANIEL BOVET, chef du Laboratoire de chimie thérapeutique de l'Istituto superiore di sanità, à Rome. Il couronne une œuvre scientifique aussi importante par ses aspects théoriques et par les voies nouvelles qu'elle a ouvertes que par ses applications médicales.

Né à Neuchâtel (Suisse) en 1907, M. BOVET a fait ses études à la faculté des sciences de l'Université de Genève. A 22 ans, il entre à l'Institut Pasteur de Paris, dans le laboratoire de FOURNEAU. Il y rencontre Mlle NITTI qui deviendra sa femme et une admirable collaboratrice. C'est en 1947 que les BOVET s'établissent à Rome.

A l'Institut Pasteur, M. BOVET participe d'abord à des recherches dans le domaine de la chimiothérapie. Avec M. et Madame TRÉFOUËL et FEDERICO NITTI, il démontre en 1935 que le prontosil dont DOMAGK venait de découvrir les propriétés anti-infectieuses agit dans les tissus une scission de sa liaison azoïque et fournit la para-aminobenzène-sulfonamide. C'est cette substance qui constitue la fraction active de la molécule du prontosil et c'est d'elle que dérivent les nombreux sulfamidés dont la médecine dispose actuellement.

C'est à la pharmacologie chimique du système nerveux végétatif que M. BOVET, par la suite, consacre son

activité. Dominant avec une égale maîtrise les problèmes de la synthèse chimique et ceux de la pharmacodynamie, il effectue ses recherches les plus importantes dans le domaine des sympatholytiques, des anti-histaminiques et des poisons curarisants.

Au cours de ses recherches sur les sympatholytiques, substances bloquant les effets du système nerveux sympathique et de ses médiateurs adrénérergiques, M. BOVET rapporte dès 1933 les effets puissants de certains benzodioxanes, le 883 F (Prosypal) et le 933 F (Piperoxan). Cette dernière substance rend de précieux services dans le diagnostic des tumeurs fonctionnelles de la médullo-surrénale.

En 1937, soit plus d'un quart de siècle après que DALE eût étudié la pharmacologie de l'histamine et découvert son rôle dans le choc anaphylactique, M. BOVET et ses collaborateurs démontrent pour la première fois les propriétés anti-histaminiques de certains éthers phénoliques dont le plus actif, le 929 F, protège le cobaye contre le choc histaminique. De nombreux antagonistes de l'histamine furent ensuite étudiés par M. BOVET, en particulier un dérivé de l'aminopyrine, le néoanergan, l'un des plus puissants anti-histaminiques connus. L'utilité clinique de tels produits dans le traitement de phénomènes allergiques se révéla si grande que des milliers d'anti-histaminiques ont été synthétisés depuis lors dans de nombreux laboratoires.

Poursuivant leurs recherches sur la pharmacologie des transmissions neuro-effectrices, M. BOVET et ses collaborateurs ont fait, ces dernières années, de remarquables découvertes dans le domaine des curarisants de synthèse. C'est en effet en 1946 qu'ils réussissent la première synthèse d'une substance curarisante, réalisée sur le modèle de la *d*-tubocurarine et dont la sélectivité pour la jonction neuromusculaire est comparable à celle de cet alcaloïde naturel du curare. Une série de synthèses de structures de plus en plus simplifiées, aboutissant à la découverte du Flaxédil, permettent de préciser les caractéristiques chimiques des produits curarisants et les rapports entre leur structure et celle de l'acétylcholine, le médiateur de la transmission neuromusculaire. L'action curarisante de la succinylcholine dont la molécule est le «doublet» de celle de l'acétylcholine est également découverte. Flaxédil et succinylcholine ont pris place parmi les adjuvants les plus précieux de l'anesthésie chirurgicale car ils permettent d'obtenir une relaxation musculaire sans provoquer divers effets indésirables des alcaloïdes du curare; de plus, la durée de leur action est aisément réglable¹.

L'œuvre de M. BOVET, qui a rendu des services inestimables à la médecine dans les domaines les plus variés, revêt également une importance théorique considérable par les lumières qu'elle apporte sur les relations entre la structure chimique des composés et leurs effets. Dans la préface de leur ouvrage: *Structure et activité pharmacodynamique des médicaments du système nerveux végétatif*, M. BOVET et Mme BOVET-NITTI écrivent: «Les rapports entre la constitution chimique des corps et leur action pharmacodynamique sera, à notre sens, l'aboutissement et la justification de toute recherche pharmacodynamique.» On ne saurait mieux définir la ligne directrice de l'œuvre de M. DANIEL BOVET. J. POSTERNAK

Corrigendum

A. FREY-WYSSLING und S. BÄBLER: *Zur Biochemie des Gewächshaustabaks*. *Experientia* Vol. XIII, Heft 10, S. 399 (1957). Auf Seite 399, rechte Kolonne, gehört der zweite Abschnitt «Es scheint also ... zu stimulieren vermogen» unter die Tabelle.

¹ D. BOVET-NITTI, *Exper.* 4, 325 (1948).

¹ A. R. TODD, *Exper.* 2, 55 (1946).

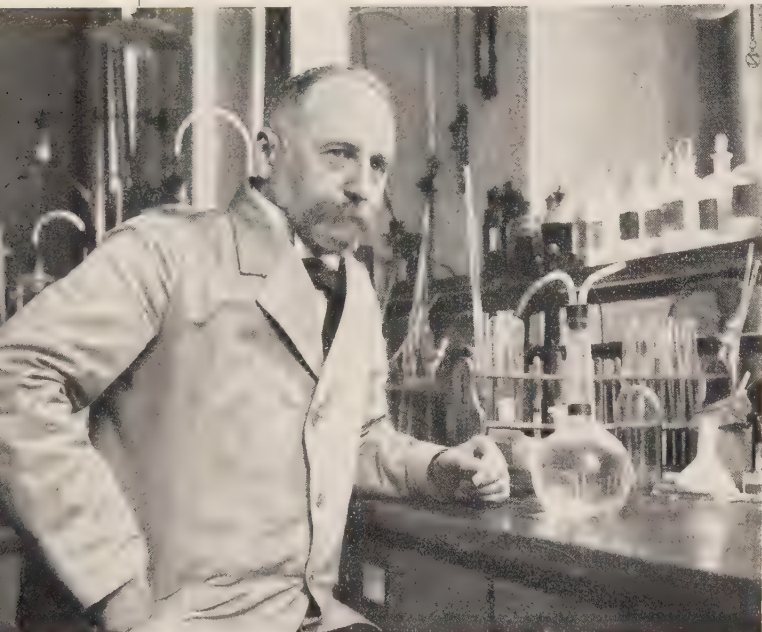
² *Reviews of pure and applied Chemistry* 1, 14 (1951).



Die pharmazeutischen
Spezialitäten «Sandoz»
sind das Ergebnis
intensiver chemischer,
pharmakologischer
und medizinischer
Forschung.
Sie geniessen
das Vertrauen
des Arztes
in der ganzen Welt.

SANDOZ A.G., BASEL

Noch vor Weihnachten erscheint eine zweite Auflage der Biographie:



RICHARD WILLSTÄTTER

Aus meinem Leben*

Von Arbeit, Musse und Freunden

Herausgegeben und mit einem
Nachwort versehen
von ARTHUR STOLL, Basel

RICHARD WILLSTÄTTER, der berühmte Chemiker und Nobelpreisträger, formte in seinem Schweizer Exil 1939–42 aus der Fülle des Durchlebten eine Biographie, die über das Wissenschaftsgeschichtliche hinaus zur Zeit- und Kulturgeschichte beitragen sollte. Dies gelang ihm wie bis heute keinem seiner Generation.

Das Buch spricht daher auch den naturwissenschaftlich nicht vorgebildeten Leser an. Es erstet das Bild eines grossen Gelehrten und Menschen, das sich leuchtend vom dunklen Hintergrund der Zeitumstände abhebt.

Ein glänzender Stilist ist hier am Werk. Scharf und ohne Retusche werden die grossen Fach- und Zeitgenossen umrissen. Zwei ausführliche Porträts sind ADOLF VON BAEYER – dem Lehrer – und FRITZ HABER – dem Freund – gewidmet.

Aus eigener Erfahrung heraus wird Grundsätzliches über Erziehung, Lehre, Forschung, ihr Verhältnis zu Industrie und Staat gesagt. Die politische Betrachtung ist konservativ, zurückhaltend in der Form, durchaus entschieden in der eigenen Haltung. Die Schilderung der Daseinsführung, der Musse, der Reisen, des Umgangs mit der bildenden Kunst erweist den geniessenden Kenner und hohe Selbstzucht zugleich. Eine Fülle plastischer Details, manche äusserst amüsant vorgetragen, lässt die Epoche lebendig werden. Darin eingebettet ist die geradezu klassische Schilderung der eigenen Leistung, die ihm bekanntlich den Nobelpreis für Chemie eintrug und alle Ehren, welche die Länder der Kulturwelt zu vergeben hatten.

Lebensweg und sittliche Grösse dieses Mannes, eines Deutschen und Juden, ergreifen und erschüttern den Leser.

*1958. 2. Auflage, VIII, ca. 470 Seiten mit einem Register, einem farbigen Titelbild und 49 Abbildungen. Ganzleinen DM 28.–



VERLAG CHEMIE · GMBH · WEINHEIM / BERGSTR.

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¹ Seules les informations les plus importantes sont indiquées. - Es sind nur die wichtigsten Informationen aufgeführt. - Si riportano
soltanto le informazioni più importanti. - Only the most important notes are cited.

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